chronic quinidine toxicity, but it may appear in sensitive patients after a single moderate dose.

A few cases of **hepatotoxicity**, including granulomatous hepatitis, have been reported in patients receiving quinidine. All of these have appeared during the first few weeks of therapy, and most (not all) have remitted once quinidine was withdrawn.

Autoimmune and inflammatory syndromes associated with quinidine therapy have included fever, urticaria, flushing, exfoliative rash, bronchospasm, psoriaform rash, pruritus and lymphadenopathy, hemolytic anemia, vasculitis, thrombocytopenic purpura, uveitis, angioedema, agranulocytosis, the sicca syndrome, arthralgia, myalgia, elevation in serum levels of skeletal-muscle enzymes, and a disorder resembling systemic lupus erythematosus.

Convulsions, apprehension, and ataxia have been reported, but it is not clear that these were not simply the results of hypotension and consequent cerebral hypoperfusion. There are many reports of syncope. Acute psychotic reactions have been reported to follow the first dose of quinidine, but these reactions appear to be extremely rare.

Other adverse reactions occasionally reported include depression, mydriasis, disturbed color perception, night blindness, scotomata, optic neuritis, visual field loss, photosensitivity, and abnormalities of pigmentation.

OVERDOSAGE

Overdoses with various oral formulations of quinidine have been well described. Death has been described after a 5-gram ingestion by a toddler, while an adolescent was reported to survive after ingesting 8 grams of quinidine.

The most important ill effects of acute quinidine overdoses are ventricular arrhythmias and hypotension. Other symptoms of overdose may include vomiting, diarrhea, tinnitus, high-frequency hearing loss, vertigo, blurred vision, diplopia, photophobia, headache, confusion and delirium.

Arrhythmias: Serum quinidine levels can be conveniently assayed and monitored, but the electrocardiographic QT_c interval is a better predictor of quinidine-induced ventricular arrhythmias.

The necessary treatment of hemodynamically unstable polymorphic ventricular tachycardia (including *torsades de pointes*) is withdrawal of treatment with quinidine and either immediate cardioversion or, if a cardiac pacemaker is in place or immediately available, immediate overdrive pacing. After pacing or cardioversion, further management must be guided by the length of the QT_c interval.

Quinidine-associated ventricular tachyarrhythmias with normal underlying QT_c intervals have not been adequately studied. Because of the theoretical possibility of QT-prolonging effects that might be additive to those of quinidine, other antiarrhythmics with Class I (disopyramide, procainamide) or Class III activities should (if possible) be avoided. Similarly, although the use of bretylium in quinidine overdose has not been reported, it is reasonable to expect that the α-blocking properties of bretylium might be additive to those of quinidine, resulting in problematic hypotension.

If the post-cardioversion QT_c interval is prolonged, then the precardioversion polymorphic ventricular tachycardia was (by definition) *torsades de pointes*. In this case, lidocaine and bretylium are unlikely to be of value, and other Class I antiarrhythmics (disopyramide, procainamide) are likely to exacerbate the situation. Factors contributing to QT_c prolongation (especially hypokalemia, hypomagnesemia, and hypocalcemia) should be sought out and (if possible) aggressively corrected. Prevention of recurrent *torsades* may require sustained overdrive pacing or the cautious administration of isoproterenal (30–150 ng/kg/min).

Hypotension: Quinidine-induced hypotension that is not due to an arrhythmia is likely to be a consequence of quinidine-related α-blockade and vasorelaxation. Simple repletion of central volume (Trendelenburg positioning, saline infusion) may be sufficient therapy; other interventions reported to have been beneficial in this setting are those that increase peripheral vascular resistance, including α-agonist catecholamines (norepinephrine, metaraminol) and the Military Anti-Shock Trousers.

Treatment:

To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison-Control Center. Telephone numbers of certified poison-control centers are listed in the Physicians' Desk Reference (PDR). In managing overdose, consider the possibilities of multiple-drug overdoses, drug-drug interactions, and unusual drug kinetics in your patient.

Accelerated removal: Adequate studies of orally-administered activated charcoal in human overdoses of quinidine have not been reported, but there are animal data showing significant enhancement of systemic elimination following this intervention, and there is at least one human case report in which the elimination half-life of quinidine in the serum was apparently shortened by repeated gastric lavage.

Activated charcoal should be avoided if an ileus is present; the conventional dose is 1 gram/kg administered every 2–6 hours as a slurry with 8 mL/kg of tap water.

Although renal elimination of quinidine might theoretically be accelerated by maneuvers to acidify the urine, such maneuvers are potentially hazardous and of no demonstrated benefit.

Quinidine is not usefully removed from the circulation by dialysis.

Following quinidine overdose, drugs that delay elimination of quinidine (cimetidine, carbonic-anhydrase inhibitors, thiazide diuretics) should be withdrawn unless absolutely required.

DOSAGE AND ADMINISTRATION

The dose of quinidine delivered by QUINAGLUTE DURA-TABS® tablets may be titrated by breaking a tablet in half. If tablets are crushed or chewed, their sustained-release properties will be lost.

The dosage of quinidine varies considerably depending upon the general condition and the cardiovascular state of the patient.

Conversion of atrial fibrillation/flutter to sinus rhythm

Especially in patients with known structural heart disease or other risk factors for toxicity, initiation or dose-adjustment of treatment with QUINAGLUTE® should generally be performed in a setting where facilities and personnel for monitoring and resuscitation are continuously available.

Patients with symptomatic atrial fibrillation/flutter should be treated with QUINAGLUTE® only after ventricular rate control (e.g., with digitalis or β-blockers) has failed to provide satisfactory control of symptoms.

Adequate trials have not identified an optimal regimen of QUINAGLUTE® for conversion of atrial fibrillation/flutter to sinus rhythm. In one reported regimen, the patient first receives two tablets (648 mg; 403 mg of quinidine base) of QUINAGLUTE® every eight hours. If this regimen has not resulted in conversion after 3 or 4 doses, then the dose is cautiously increased. If, at any point during administration, the QRS complex widens to 130% of its pre-treatment duration; the QT_c interval widens to 130% of its pre-treatment duration and is then longer than 500 ms; P waves disappear; or the patient develops significant tachycardia, symptomatic bradycardia, or hypotension, then QUINAGLUTE® is discontinued, and other means of conversion (e.g., direct-current cardioversion) are considered.

In another regimen sometimes used, the patient receives one tablet (324 mg; 202 mg of quinidine base) every eight hours for two days; then two tablets every twelve hours for two days; and finally two tablets every eight hours for up to four days. The four-day stretch may come at one of the lower doses if, in the judgment of the physician, the lower dose is the highest one that will be tolerated. The criteria for discontinuation of treatment with QUINAGLUTE® are the same as in the other regimen.

Reduction in the frequency of relapse into atrial fibrillation/flutter

In a patient with a history of frequent symptomatic episodes of atrial fibrillation/flutter, the goal of therapy with QUINAGLUTE® should be an increase in the average time between episodes. In most patients, the tachyarrhythmia *will recur* during therapy with QUINAGLUTE®, and a single recurrence should not be interpreted as therapeutic failure.

Especially in patients with known structural heart disease or other risk factors for toxicity, initiation or dose adjustment of treatment with QUINAGLUTE® should generally be performed in a setting where facilities and personnel for monitoring and resuscitation are continously available.

Monitoring should be continued for two or three days after initiation of the regimen on which the patient will be discharged.

Therapy with QUINAGLUTE® should be begun with one tablet (324 mg; 202 mg of quinidine base) every eight or twelve hours. If this regimen is well tolerated, and if the serum quinidine level is still well within the laboratory's therapeutic range, and if the average time between arrhythmic episodes has not been satisfactorily increased, then the dose may be cautiously raised. The total daily dosage should be reduced if the QRS complex widens to 130% of its pre-treatment duration; the QT_c interval widens to 130% of its pre-treatment duration and is then longer than 500 ms; P waves disappear; or the patient develops significant tachycardia, symptomatic bradycardia, or hypotension.

Suppression of life-threatening ventricular arrhythmias

Dosing regimens for the use of quinidine gluconate in suppressing life-threatening ventricular arrhythmias have not been adequately studied. Described regimens have generally been similar to the regimen described just above for the prophylaxis of symptomatic atrial fibrillation/flutter. Where possible, therapy should be guided by the results of programmed eletrical stimulation and/or Holter monitoring with exercise.

HOW SUPPLEID

QUINAGLUTE DURA-TABS® tablets are 324 mg white to off-white, round tablets embossed with C in a flask design on one side and with a clock-like design on the other.

[See Figure at top of next column.]

The tablets are available in bottles and unit-dose packages as follows:

bottle of 100	NDC 50419-101-10
bottle of 250	NDC 50419-101-25
bottle of 500	NDC 50419-101-50
unit-dose box of 100	NDC 50419-101-11

Store tablets at controlled room temperature (15–30°C; 59–86°F).

CAUTION: Federal (USA) law prohibits dispensing without prescription.

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BERLEX® Laboratories, Wayne, NJ 07470

Rev. 12/94 60695-0

Shown in Product Identification Guide, page 306

TRI-LEVLEN® 21 ℞

[trī-lēvlĕn]

Tablets

(levonorgestrel and ethinyl estradiol tablets—triphasic regimen)

TRI-LEVLEN® 28 ℞

[trī-lēvlĕn]

Tablets

(levonorgestrel and ethinyl estradiol tablets—triphasic regimen)

LEVLEN® 21 ℞

[lēvlĕn]

Tablets

(levonorgestrel and ethinyl estradiol tablets)

LEVLEN® 28 ℞

[lēvlĕn]

Tablets

(levonorgestrel and ethinyl estradiol tablets)

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

TRI-LEVLEN® 21 tablets

Each cycle of TRI-LEVLEN® 21 (Levonorgestrel and Ethinyl Estradiol Tablets—Triphasic Regimen) tablets consists of three different drug phases as follows: Phase 1 comprised of 6 brown film-coated tablets, each containing 0.050 mg of levonorgestrel (d(-)-13 beta-ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one), a totally synthetic progestogen, and 0.030 mg of ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol); phase 2 comprised of 5 white film-coated tablets, each containing 0.075 mg levonorgestrel and 0.040 mg ethinyl estradiol; and, phase 3 comprised of 10 light-yellow film-coated tablets, each containing 0.125 mg levonorgestrel and 0.030 mg ethinyl estradiol. The inactive ingredients present are cellulose, iron oxides, lactose, magnesium stearate, polacrilin potassium, polyethylene glycol, titanium dioxide, and hydroxypropyl methylcellulose.

TRI-LEVLEN® 28 tablets

Each cycle of TRI-LEVLEN® 28 (Levonorgestrel and Ethinyl Estradiol Tablets—Triphasic Regimen) tablets consists of three different drug phases as follows: Phase 1 comprised of 6 brown film-coated tablets, each containing 0.050 mg of levonorgestrel (d(-)-13 beta-ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one), a totally synthetic progestogen, and 0.030 mg of ethinyl estradiol (19-nor-17 α-pregna-1,3,5(10)-trien-20-yne-3, 17-diol); phase 2 comprised of 5 white film-coated tablets, each containing 0.075 mg levonorgestrel and 0.040 mg ethinyl estradiol; and phase 3 comprised of 10 light-yellow film-coated tablets, each containing 0.125 mg levonorgestrel and 0.030 mg ethinyl estradiol; then followed by 7 light-green film-coated inert tablets. The inactive ingredients present are cellulose, F D & C Blue 1, iron oxides, lactose, magnesium stearate, polacrilin potassium, poly-

Continued on next page

Information on the Berlex products appearing here is based on the most current information available at the time of publication closing. Further information for these and other products may be obtained from the Medical Affairs Department, Berlex Laboratories, 300 Fairfield Road, Wayne, New Jersey 07470, 1-800-888-2407. Information on Betaseron and Fludara may be obtained from Berlex Laboratories, 15049 San Pablo Avenue, Richmond, California 94804-0016, 1-800-888-4112.

Berlex Laboratories—Cont.

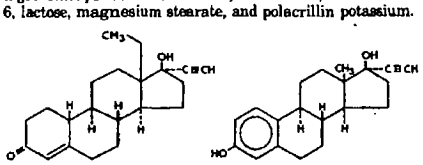
ethylene glycol, titanium dioxide, and hydroxypropyl methylcellulose.

LEVLEN® 21 tablets:

Each LEVLEN® 21 tablet (Levonorgestrel and Ethinyl Estradiol Tablets) contains 0.15 mg of levonorgestrel (d(-)-13 beta-ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one), a totally synthetic progestogen, and 0.03 mg of ethinyl estradiol (19-nor-17 α-pregna-1,3,5(10)-trien-20-yne-3, 17-diol). The inactive ingredients present are cellulose, FD&C Yellow 6, lactose, magnesium stearate, and polacrillin potassium.

LEVLEN® 28 tablets:

21 light-orange LEVLEN® tablets (Levonorgestrel and Ethinyl Estradiol Tablets), each containing 0.15 mg of levonorgestrel (d(-)-13 beta-ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one), a totally synthetic progestogen, and 0.03 mg of ethinyl estradiol (19-nor-17 α-pregna-1,3,5(10)-trien-20-yne-3, 17-diol), and 7 pink inert tablets. The inactive ingredients present are cellulose, D&C Red 30, FD&C Yellow 6, lactose, magnesium stearate, and polacrillin potassium.



Levonorgestrel Ethinyl Estradiol

CLINICAL PHARMACOLOGY

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

INDICATIONS AND USAGE

Oral contraceptives are indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception.

Oral contraceptives are highly effective. Table I lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization and the IUD, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

TABLE I: LOWEST EXPECTED AND TYPICAL FAILURE RATES DURING THE FIRST YEAR OF CONTINUOUS USE OF A METHOD

% of Women Experiencing an Accidental Pregnancy in the First Year of Continuous Use

Method	Lowest Expected*	Typical**
(No Contraception)	(85)	(85)
Oral contraceptives		3
combined	0.1	N/A***
progestin only	0.5	N/A***
Diaphragm with spermicidal cream or jelly	6	18
Spermicides alone (foam, and vaginal suppositories)	3	21
Vaginal Sponge		
nulliparous	6	18
multiparous	9	28
Depo-Provera (injectable progestogen)	0.3	0.3
NORPLANT® SYSTEM (implants)	0.2#	0.2#
IUD		3
progesterone	2	N/A***
copper T 380A	0.8	N/A***
Condom without spermicides	2	12
Periodic abstinence	1–9	20
Female sterilization	0.2	0.4
Male sterilization	0.1	0.15

Adapted from J. Trussell et al., Table I. Studies in Family Planning, *21(1)*: Jan.-Feb. 1990.

* The authors' best guess of the percentage of women expected to experience an accidental pregnancy among couples who initiate a method (not necessarily for the first time) and who use it consistently and correctly during the first year if they do not stop use for any other reason.

** This term represents "typical" couples who initiate use of a method (not necessarily for the first time), who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

*** N/A—Data not available.

This data is based on Norplant System clinical trials.

CONTRAINDICATIONS

Oral contraceptives should not be used in women with any of the following conditions:

- Thrombophlebitis or thromboembolic disorders.
- A past history of deep-vein thrombophlebitis or thromboembolic disorders.
- Cerebral-vascular or coronary-artery disease.
- Known or suspected carcinoma of the breast.
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal genital bleeding.
- Cholestatic jaundice of pregnancy or jaundice with prior pill use.
- Hepatic adenomas or carcinomas.
- Known or suspected pregnancy.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral-contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, gallbladder disease, and hypertension, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is based principally on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of disease, namely, a ratio of the incidence of a disease among oral-contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral-contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiological methods.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. *Myocardial Infarction*

An increased risk of myocardial infarction has been attributed to oral-contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary-artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral-contraceptive users has been estimated to be two to six. The risk is very low under the age of 30.

Smoking in combination with oral-contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 (Table II) among women who use oral contraceptives.

[See Table II at top of next column.]

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see section 9 in "WARNINGS"). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. *Thromboembolism*

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate post partum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four to six weeks after delivery in women who elect not to breast-feed, or a midtrimester pregnancy termination.

c. *Cerebrovascular diseases*

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (> 35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.

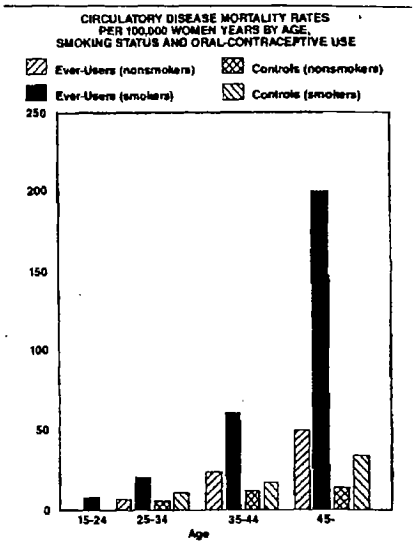
In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

d. *Dose-related risk of vascular disease from oral contraceptives*

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New accep-

TABLE II. (Adapted from P.M. Layde and V. Beral, Lancet, *1*:541–546, 1981.)



tors of oral-contraceptive agents should be started on preparations containing less than 50 mcg of estrogen.

e. Persistence of risk of vascular disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40–49 years who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 micrograms or higher of estrogens.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table III). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral-contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is less than that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral-contraceptive users is based on data gathered in the 1970's—but not reported until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral-contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral-contraceptive use after age 40 in healthy nonsmoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. Therefore, the Committee recommended that the benefits of oral-contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take oral contraceptives, should take the lowest possible dose formulation that is effective.

[See table III above.]

3. CARCINOMA OF THE REPRODUCTIVE ORGANS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. The overwhelming evidence in the literature suggests that use of oral contraceptives is not associated with an increase in the risk of developing breast cancer, regardless of the age and parity of first use or with most of the marketed brands and doses. The Cancer and Steroid Hormone (CASH) study also showed no latent effect on the risk of breast cancer for at least a decade following long-term use. A few studies have shown a slightly increased relative risk of developing breast cancer, although the methodology of these studies, which included differences in examination of users and nonusers and differences in age at start of use, has been questioned.

Some studies suggest that oral-contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral-contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral-contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) oral-contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral-contraceptive users approaches less than one per million users.

5. OCULAR LESIONS

There have been clincial case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

TABLE III—ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE

Method of control and outcome	15–19	20–24	25–29	30–34	35–39	40–44
No fertility—control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives nonsmoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth related
** Deaths are method related

Adapted from H.W. Ory, Family Planning Perspectives *15* :57–63, 1983.

6. ORAL-CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral-contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral-contraceptive use should be discontinued if pregnancy is confirmed.

7. GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral-contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral-contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 micrograms of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see "WARNINGS" 1a. and 1d.), changes in serum triglycerides and lipoprotein levels have been reported in oral-contraceptive users.

9. ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral-contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing quantities of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women with hypertertension elect to use oral contraceptives, they should be monitored closely, and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension among ever- and never-users.

10. HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent, or severe requires discontinuation of oral contraceptives and evaluation of the cause.

11. BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. The type and dose of progestogen may be important. Nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

PRECAUTIONS

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

1. PHYSICAL EXAMINATION AND FOLLOW UP

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of oral contraceptives and at least annually during use of oral contraceptives. These physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

2. LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult. (See "WARNINGS" 1d.)

3. LIVER FUNCTION

If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

4. FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

5. EMOTIONAL DISORDERS

Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related. Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

6. CONTACT LENSES

Contact-lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

7. DRUG INTERACTIONS

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and possibly with griseofulvin, ampicillin, and tetracyclines.

Continued on next page

Information on the Berlex products appearing here is based on the most current information available at the time of publication closing. Further information for these and other products may be obtained from the Medical Affairs Department, Berlex Laboratories, 300 Fairfield Road, Wayne, New Jersey 07470, 1-800-888-2407. Information on Betaseron and Fludara may be obtained from Berlex Laboratories, 15049 San Pablo Avenue, Richmond, California 94804-0016, 1-800-888-4112.

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8. INTERACTIONS WITH LABORATORY TESTS
Certain endocrine and liver-function tests and blood components may be affected by oral contraceptives:
a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
b. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
c. Other binding proteins may be elevated in serum.
d. Sex-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.
e. Triglycerides may be increased.
f. Glucose tolerance may be decreased.
g. Serum folate levels may be depressed by oral-contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.
9. CARCINOGENESIS
See "WARNINGS" section.
10. PREGNANCY
Pregnancy Category X. See "CONTRAINDICATIONS" and "WARNINGS" sections.
11. NURSING MOTHERS
Small amounts of oral-contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

INFORMATION FOR THE PATIENT
See "Patient Labeling" printed below.

ADVERSE REACTIONS
An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see "WARNINGS" section).

- Thrombophlebitis
- Aterial thromboembolism
- Pulmonary embolism
- Myocardial infarction
- Cerebral hemorrhage
- Cerebral thrombosis
- Hypertension
- Gallbladder disease
- Hepatic adenomas or benign liver tumors

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:
- Mesenteric thrombosis
- Retinal thrombosis

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related:
- Nausea
- Vomiting
- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea
- Temporary infertility after discontinuation of treatment
- Edema
- Melasma which may persist
- Breast changes: tenderness, enlargement, and secretion
- Change in weight (increase or decrease)
- Change in cervical erosion and cervical secretion
- Diminution in lactation when given immediately postpartum
- Cholestatic jaundice
- Migraine
- Rash (allergic)
- Mental depression
- Reduced tolerance to carbohydrates
- Vaginal candidiasis
- Change in corneal curvature (steepening)
- Intolerance to contact lenses

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted:
- Congenital anomalies
- Premenstrual syndrome
- Cataracts
- Changes in appetitie
- Cystitis-like syndrome
- Headache
- Nervousness
- Dizziness
- Hirsutism
- Loss of scalp hair
- Erythema nodosum
- Hemorrhagic eruption
- Vaginitis
- Porphyria
- Impaired renal function
- Hemolytic uremic syndrome
- Budd-Chiari syndrome
- Acne
- Erythema multiforme
- Cerebral-vascular disease
- with mitral valve prolapse
- Lupus-like Syndromes
- Changes in libido
- Colitis
- Sickle-Cell Disease

OVERDOSAGE
Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

NONCONTRACEPTIVE HEALTH BENEFITS
The following noncontraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral-contraceptive formulations containing doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol.
Effects on menses:
- increased menstrual cycle regularity
- decreased blood loss and decreased incidence of iron deficiency anemia
- decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation:
- decreased incidence of functional ovarian cysts
- decreased incidence of ectopic pregnancies

Effects from long-term use:
- decreased incidence of fibroadenomas and fibrocystic disease of the breast
- decreased incidence of acute pelvic inflammatory disease
- decreased incidence of endometrial cancer
- decreased incidence of ovarian cancer

DOSAGE AND ADMINISTRATION
TRI-LEVLEN® 21 Tablets
To achieve maximum contraceptive effectiveness, TRI-LEVLEN® 21 Tablets (levonorgestrel and ethinyl estradiol tablets—triphasic regimen) should be taken exactly as directed and at intervals not exceeding 24-hours.
TRI-LEVLEN® 21 Tablets are a three-phase preparation. The dosage of TRI-LEVLEN® 21 Tablets is **one tablet** daily for 21 consecutive days per menstrual cycle in the following order: 6 brown tablets (phase 1), followed by 5 white tablets (phase 2), and then followed by the last 10 light-yellow tablets (phase 3), according to the prescribed schedule. Tablets are then discontinued for 7 days (three weeks on, one week off).
It is recommended that TRI-LEVLEN® 21 Tablets be taken at the same time each day. During the first cycle of medication, the patient should be instructed to take one TRI-LEVLEN® 21 Tablet daily in the order of 6 brown, 5 white and, finally, 10 light-yellow tablets for twenty-one (21) consecutive days, beginning on day one (1) of her menstrual cycle. (The first day of menstruation is day one.) The tablets are then discontinued for one week (7 days). Withdrawal bleeding usually occurs within 3 days following discontinuation of TRI-LEVLEN® 21 Tablets. (If an alternate starting regimen is used [Sunday Start or postpartum], contraceptive reliance should not be placed on TRI-LEVLEN® 21 Tablets until after the first 7 consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered.)
The patient begins her next and all subsequent 21-day courses of TRI-LEVLEN® 21 Tablets on the same day of the week that she began her first course, following the same schedule: 21 days on—7 days off. She begins taking her brown tablets on the 8th day after discontinuance, regardless of whether or not a menstrual period has occurred or is still in progress. Any time the next cycle of TRI-LEVLEN® 21 Tablets is started later than the 8th day, the patient should be protected by another means of contraception until she has taken a tablet daily for seven consecutive days.
If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician. Although the occurrence of pregnancy is highly unlikely if TRI-LEVLEN® 21 Tablets are taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed one or more tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.
The risk of pregnancy increases with each active (brown, white, or light-yellow) tablet missed. For additional patient instructions regarding missed pills, see the "WHAT TO DO IF YOU MISS PILLS" section in the DETAILED PATIENT LABELING below. If breakthrough bleeding occurs following missed active tablets, it will usually be transient and of no consequence. If the patient misses one or more light-green tablets, she is still protected against pregnancy **provided** she begins taking brown tablets again on the proper day.
In the nonlactating mother, TRI-LEVLEN® 21 Tablets may be initiated postpartum, for contraception. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See "CONTRAINDICATIONS", "WARNINGS", and "PRECAUTIONS" concerning thromboembolic disease.) It is to be noted that early resumption of ovulation may occur if Parlodel® (bromocriptine mesylate) has been used for the prevention of lactation.
TRI-LEVLEN® 28 Tablets
To achieve maximum contraceptive effectiveness, TRI-LEVLEN® 28 Tablets (levonorgestrel and ethinyl estradiol tablets—triphasic regimen) should be taken exactly as directed and at intervals not exceeding 24-hours.
TRI-LEVLEN® 28 Tablets are a three-phase preparation plus 7 inert tablets. The dosage of TRI-LEVLEN® 28 Tablets is one tablet daily for 28 consecutive days per menstrual cycle in the following order: 6 brown tablets (phase 1), followed by 5 white tablets (phase 2), followed by 10 light-yellow tablets (phase 3), plus 7 light-green inert tablets according to the prescribed schedule.
It is recommended that TRI-LEVLEN® 28 Tablets be taken at the same time each day. During the first cycle of medication, the patient should be instructed to take one TRI-LEVLEN® 28 Tablet daily in the order of 6 brown, 5 white, 10 light-yellow tablets and then 7 light-green inert tablets for twenty-eight (28) consecutive days, beginning on day one (1) of her menstrual cycle. (The first day of menstruation is day one.) Withdrawal bleeding usually occurs within 3 days following the last light-yellow tablet. (If an alternate starting regimen is used [Sunday Start or postpartum], contraceptive reliance should not be placed on TRI-LEVLEN® 28 Tablets until after the first 7 consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered.)
The patient begins her next and all subsequent 28-day courses of TRI-LEVLEN® 28 Tablets on the same day of the week that she began her first course, following the same schedule. She begins taking her brown tablets on the next day after ingestion of the last light-green tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Any time a subsequent cycle of TRI-LEVLEN® 28 Tablets is started later than the next day, the patient should be protected by another means of contraception until she has taken a tablet daily for seven consecutive days.
If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician. Although the occurrence of pregnancy is highly unlikely if TRI-LEVLEN® 28 Tablets are taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed one or more active tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.
The risk of pregnancy increases with each active (brown, white, or light-yellow) tablet missed. For additional patient instructions regarding missed pills, see the "WHAT TO DO IF YOU MISS PILLS" section in the DETAILED PATIENT LABELING below. If breakthrough bleeding occurs following missed active tablets, it will usually be transient and of no consequence. If the patient misses one or more light-green tablets, she is still protected against pregnancy **provided** she begins taking brown tablets again on the proper day.
In the nonlactating mother, TRI-LEVLEN® 28 Tablets may be initiated postpartum, for contraception. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See "CONTRAINDICATIONS", "WARNINGS", and "PRECAUTIONS" concerning thromboembolic disease.) It is to be noted that early resumption of ovulation may occur if Parlodel® (bromocriptine mesylate) has been used for the prevention of lactation.
LEVLEN® 21 Tablets
To achieve maximum contraceptive effectiveness, LEVLEN® 21 Tablets (levonorgestrel and ethinyl estradiol tablets) should be taken exactly as directed and at intervals not exceeding 24-hours.
The dosage of LEVLEN® 21 Tablets is **one tablet** daily for 21 consecutive days per menstrual cycle according to the prescribed schedule. Tablets are then discontinued for 7 days (three weeks on, one week off).
It is recommended that LEVLEN® 21 Tablets be taken at the same time each day. During the first cycle of medication, the patient should be instructed to take one LEVLEN® 21 Tablet daily for twenty-one (21) consecutive days, beginning on day one (1) of her menstrual cycle. (The first day of menstruation is day one.) The tablets are then discontinued for one week (7 days). Withdrawal bleeding usually occurs

within 3 days following discontinuation of LEVLEN® 21 Tablets. (If an alternate starting regimen is used [Sunday Start or postpartum], contraceptive reliance should not be placed on LEVLEN® 21 Tablets until after the first 7 consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered.)

The patient begins her next and all subsequent 21-day courses of LEVLEN® 21 Tablets on the same day of the week that she began her first course, following the same schedule: 21 days on—7 days off. She begins taking her light-orange tablets on the 8th day after discontinuance, regardless of whether or not a menstrual period has occurred or is still in progress. Any time the next cycle of LEVLEN® 21 Tablets is started later than the 8th day, the patient should be protected by another means of contraception until she has taken a tablet daily for seven consecutive days.

If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician. Although the occurrence of pregnancy is highly unlikely if LEVLEN® 21 Tablets are taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed one or more tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

Any time the patient misses two or more tablets, she should also use another method of contraception until she has taken a tablet daily for seven consecutive days. If breakthrough bleeding occurs following missed active tablets, it usually will be transient and of no consequence. If the patient misses one or more pink tablets, she is still protected against pregnancy provided she begins taking the light-orange tablets again on the proper day.

In the nonlactating mother, LEVLEN® 21 Tablets may be initiated postpartum, for contraception. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See "CONTRAINDICATIONS", "WARNINGS", and "PRECAUTIONS" concerning thromboembolic disease.)

LEVLEN® 28 Tablets

To achieve maximum contraceptive effectiveness, LEVLEN® 28 Tablets (levonorgestrel and ethinyl estradiol tablets) should be taken exactly as directed at intervals not exceeding 24-hours.

The dosage of LEVLEN® 28 Tablets is one light-orange tablet daily for 21 consecutive days per menstrual cycle, followed by 7 inert tablets according to the prescribed schedule. It is recommended that LEVLEN® 28 Tablets be taken at the same time each day. During the first cycle of medication, the patient should be instructed to take one LEVLEN® 28 Tablet daily in light-orange and then 7 light-green inert tablets for twenty-eight (28) consecutive days, beginning on day one (1) of her menstrual cycle. (The first day of menstruation is day one.) Withdrawal bleeding usually occurs within 3 days following the last light-orange tablet. (If an alternate starting regimen is used [Sunday Start or postpartum], contraceptive reliance should not be placed on LEVLEN® 28 Tablets until after the first 7 consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered.)

The patient begins her next and all subsequent 28-day courses of LEVLEN® 28 Tablets on the same day of the week that she began her first course, following the same schedule. She begins taking her light-orange tablets on the next day after ingestion of the last pink tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Any time a subsequent cycle of LEVLEN® 28 Tablets is started later than the next day, the patient should be protected by another means of contraception until she has taken a tablet daily for seven consecutive days.

If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician. Although the occurrence of pregnancy is highly unlikely if LEVLEN® 28 Tablets are taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed one or more active tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

Any time the patient misses two or more tablets, she should also use another method of contraception until she has taken a tablet daily for seven consecutive days. If breakthrough bleeding occurs following missed active tablets, it usually will be transient and of no consequence. If the patient misses one or more pink tablets, she is still protected against pregnancy provided she begins taking the light-orange tablets again on the proper day.

In the nonlactating mother, LEVLEN® 28 Tablets may be initiated postpartum, for contraception. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See "CONTRAINDICATIONS", "WARNINGS", and "PRECAUTIONS" concerning thromboembolic disease.)

HOW SUPPLIED

TRI-LEVLEN® 21 tablets (Levonorgestrel and Ethinyl Estradiol Tablets—Triphasic Regimen), are available in packages of 3 and 6 SLIDECASE™ dispensers. Each cycle contains 21 round, film-coated tablets as follows:

NDC 50419-195, six brown tablets marked "B" on one side and "95" on the other side, each containing 0.050 mg levonorgestrel and 0.030 mg ethinyl estradiol;

NDC 50419-196, five white to off-white tablets marked "B" on one side and "96" on the other side, each containing 0.075 mg levonorgestrel and 0.040 mg ethinyl estradiol; and

NDC 50419-197, ten light-yellow tablets marked "B" on one side and "97" on the other side, each containing 0.125 mg levonorgestrel and 0.030 mg ethinyl estradiol.

In packages of:

3 SLIDECASE™ dispensers .....NDC 50419-432-03

6 SLIDECASE™ dispensers .....NDC 50419-432-06

TRI-LEVLEN® 28 tablets (Levonorgestrel and Ethinyl Estradiol Tablets—Triphasic Regimen), are available in packages of 3 and 6 SLIDECASE™ dispensers. Each cycle contains 28 round, film-coated tablets as follows:

NDC 50419-195, six brown tablets marked "B" on one side and "95" on the other side, each containing 0.050 mg levonorgestrel and 0.030 mg ethinyl estradiol;

NDC 50419-196, five white to off-white tablets marked "B" on one side and "96" on the other side, each containing 0.075 mg levonorgestrel and 0.040 mg ethinyl estradiol;

NDC 50419-197, ten light-yellow tablets marked "B" on one side and "97" on the other side, each containing 0.125 mg levonorgestrel and 0.030 mg ethinyl estradiol; and

NDC 50419-111, seven light-green inert tablets marked "B" on one side and "11" on the other side.

In packages of:

3 SLIDECASE™ dispensers .....NDC 50419-433-03

6 SLIDECASE™ dispensers .....NDC 50419-433-06

LEVLEN® 21 tablets (Levonorgestrel and Ethinyl Estradiol Tablets), are available in packages of 3 SLIDECASE™ dispensers. Each cycle contains 21 round, tablets as follows:

NDC 50419-021, 21 active, light-orange tablets marked "B" on one side and "21" on the other side, each containing 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol;

In packages of:

3 SLIDECASE™ dispensers .....NDC 50419-410-21

LEVLEN® 28 tablets (Levonorgestrel and Ethinyl Estradiol Tablets), are available in packages of 3 SLIDECASE™ dispensers. Each cycle contains 28 round tablets as follows:

NDC 50419-021, 21 active, light-orange tablets marked "B" on one side and "21" on the other side, each containing 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol;

NDC 50419-028, 7 inert pink tablets marked "B" on one side and "28" on the other side.

In packages of:

3 SLIDECASE™ dispensers .....NDC 50419-411-28

REFERENCES

References furnished upon request.

BRIEF SUMMARY PATIENT PACKAGE INSERT

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Oral contraceptives, also known as "birth control pills" or "the pill," are taken to prevent pregnancy and when taken correctly, have a failure rate of less than 1% per year when used without missing any pills. The typical failure rate of large numbers of pill users is less than 3% per year when women who miss pills are included. For most women oral contraceptives are also free of serious or unpleasant side effects. However, forgetting to take pills considerably increases the chances of pregnancy.

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be life-threatening or may cause temporary or permanent disability or death. The risks associated with taking oral contraceptives increase significantly if you:

- smoke
- have high blood pressure, diabetes, high cholesterol
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice or malignant or benign liver tumors

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. These side effects, especially nausea, and vomiting, may subside within the first three months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and do not smoke. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences.
2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the detailed leaflet given to you with your supply of pills. Notify your doctor or health-care provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants and some antibiotics may decrease oral contraceptive effectiveness.

Studies to date of women taking the pill have not shown an increase in the incidence of cancer of the breast or cervix. There is, however, insufficient evidence to rule out the possibility that pills may cause such cancers.

Taking the pill provides some important noncontraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your health-care provider. Your health-care provider will take a medical and family history before prescribing oral contraceptives and will examine you.

You should be reexamined at least once a year while taking oral contraceptives. The "Detailed Patient Labeling" gives you further information which you should read and discuss with your health-care provider.

DETAILED PATIENT LABELING

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

INTRODUCTION

Any woman who considers using oral contraceptives (the "birth control pill" or the "pill") should understand the benefits and risks of using this form of birth control. This leaflet will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this leaflet is not a replacement for a careful discussion between you and your health-care provider. You should discuss the information provided in this leaflet with him or her, both when you first start taking the pill and during your revisits. You should also follow your health-care provider's advice with regard to regular check-ups while you are on the pill.

Continued on next page

Information on the Berlex products appearing here is based on the most current information available at the time of publication closing. Further information for these and other products may be obtained from the Medical Affairs Department, Berlex Laboratories, 300 Fairfield Road, Wayne, New Jersey 07470, 1-800-888-2407. Information on Betaseron and Fludara may be obtained from Berlex Laboratories, 15049 San Pablo Avenue, Richmond, California 94804-0016, 1-800-888-4112.

Berlex Laboratories—Cont.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives or "birth control pills" or "the pill" are used to prevent pregnancy and are more effective than other nonsurgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% when used perfectly, without missing pills.

Typical failure rates are less than 3.0% per year. The chance of becoming pregnant increases with each missed pill during the menstrual cycle.

In comparison, typical failure rates for other nonsurgical methods of birth control during the first year of use are as follows:

Implant	<1%
Injection (Depo-Provera)	<1%
IUD	3%
Diaphragm with spermicides	18%
Spermicides alone	21%
Vaginal sponge	18%-28%
Condom alone	12%
Periodic abstinence	20%
No methods	85%

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral-contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Some women should not use the pill. For example, you should not take the pill if you are pregnant or think you may be pregnant. You should also not use the pill if you have had any of the following conditions:

- Heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes
- Blood clots in the deep veins of your legs
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina
- Liver tumor (benign or cancerous)

Or, if you have any of the following:

- Chest pain (angina pectoris)
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor)
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Known or suspected pregnancy

Tell your health-care provider if you have ever had any of these conditions. Your health-care provider can recommend another method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your health-care provider if you or any family member has ever had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast x-ray or mammogram
- Diabetes
- Elevated cholesterol or triglycerides
- High blood pressure
- Migraine or other headaches or epilepsy
- Mental depression
- Gallbladder, heart or kidney disease
- History of scanty or irregular menstrual periods

Women with any of these conditions should be checked often by their health-care provider if they choose to use oral contraceptives. Also, be sure to inform your doctor or health-care provider if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES

1. RISK OF DEVELOPING BLOOD CLOTS

Blood clots and blockage of blood vessels are the most serious side effects of taking oral contraceptives and can be fatal. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping oral contraceptives three to four weeks before surgery and not taking oral contraceptives for 2 weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby or a midtrimester pregnancy termination. It is advisable to wait for at least 4 weeks after delivery if you are not breast-feeding. If you are breast-feeding, you should wait until you have weaned your child before using the pill. (See also the section on Breast-Feeding in "GENERAL PRECAUTIONS".)

2. HEART ATTACKS AND STROKES

Oral contraceptives may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.

Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.

3. GALLBLADDER DISEASE

Oral-contraceptive users probably have a greater risk than nonusers of having gallbladder disease, although this risk may be related to pills containing high doses of estrogens.

4. LIVER TUMORS

In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, a possible but not definite association has been found with the pill and liver cancers in two studies, in which a few women who developed these very rare cancers were found to have used oral contraceptives for long periods. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.

5. CANCER OF THE REPRODUCTIVE ORGANS

There is, at present, no confirmed evidence that oral contraceptives increase the risk of cancer of the reproductive organs in human studies. Several studies have found no overall increase in the risk of developing breast cancer. However, women who use oral contraceptives and have a strong family history of breast cancer or who have breast nodules or abnormal mammograms should be closely followed by their doctors.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives.

ESTIMATED RISK OF DEATH FROM A BIRTH-CONTROL METHOD OR PREGNANCY

All methods of birth control and pregnancy are associated with a risk of developing certain diseases which may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table. [See table below.]

In the above table, the risk of death from any birth-control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7 to 26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, except for those women over the age of 40 when the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who don't smoke should not take oral contraceptives is based on information from older high-dose pills and on less-selective use of pills than is practiced today. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of oral-contraceptive use by healthy, nonsmoking women over 40 years of age may outweigh the possible risks. However, all women, especially older women, are cautioned to use the lowest-dose pill that is effective.

ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE

Method of control and outcome	15–19	20–24	25–29	30–34	35–39	40–44
No fertility-control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives nonsmoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth related
** Deaths are method related

WARNING SIGNALS

If any of these adverse effects occur while you are taking oral contraceptives, call your doctor immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung).
- Pain in the calf (indicating a possible clot in the leg).
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack).
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke).
- Sudden partial or complete loss of vision (indicating a possible clot in the eye).
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or health-care provider to show you how to examine your breasts).
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor).
- Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression).
- Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-colored urine, or light-colored bowel movements (indicating possible liver problems).

SIDE EFFECTS OF ORAL CONTRACEPTIVES

1. VAGINAL BLEEDING

Irregular vaginal bleeding or spotting may occur while you are taking the pills. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle or lasts for more than a few days, talk to your doctor or health-care provider.

2. CONTACT LENSES

If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your doctor or health-care provider.

3. FLUID RETENTION

Oral contraceptives may cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your doctor or health-care provider.

4. MELASMA

A spotty darkening of the skin is possible, particularly of the face.

5. OTHER SIDE EFFECTS

Other side effects include change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, and vaginal infections.

If any of these side effects bother you, call your doctor or health-care provider.

GENERAL PRECAUTIONS

1. Missed periods and use of oral contraceptives before or during early pregnancy.

There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your health-care provider before doing so. If you have not taken the pills daily as instructed and missed a menstrual period, or if you missed two consecutive menstrual periods, you may be pregnant. Check with your health-care provider immediately to determine whether you are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of contraception.

There is no conclusive evidence that oral contraceptive use is associated with an increase in birth defects, when taken inadvertently during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these studies have not been confirmed. Nevertheless, oral contraceptives or any other drugs should not be used during pregnancy unless clearly necessary and prescribed by your doctor. You should check with

your doctor about risks to your unborn child of any medication taken during pregnancy.

2. While breast-feeding

If you are breast-feeding, consult your doctor before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, oral contraceptives may decrease the amount and quality of your milk. If possible, do not use oral contraceptives while breast-feeding. You should use another method of contraception since breast-feeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breast-feed for longer periods of time. You should consider starting oral contraceptives only after you have weaned your child completely.

3. Laboratory tests

If you are scheduled for any laboratory tests, tell your doctor you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

4. Drug interactions

Certain drugs may interact with birth control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital) and phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand) and possibly certain antibiotics. You may need to use an additional method of contraception during any cycle in which you take drugs that can make oral contraceptives less effective.

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as Chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and Syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

TRI-LEVLEN® and LEVLEN® Tablets

BEFORE YOU START TAKING YOUR PILLS:

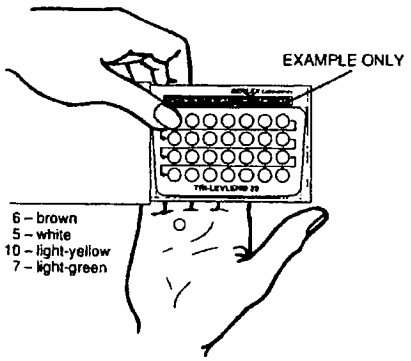
1. BE SURE TO READ THESE DIRECTIONS:
   Before you start taking your pills.
   Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
   If you miss pills you could get pregnant. This includes starting the pack late.
   The more pills you miss, the more likely you are to get pregnant.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS.
   If you do feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.
   On the days you take 2 pills, to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well.
   Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

BEFORE YOU START TAKING YOUR PILLS

TRI-LEVLEN® Tablets

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
   It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 21 OR 28 PILLS:
   The 21-pill pack has 21 "active" (6 brown, 5 white and 10 light-yellow) pills (with hormones) to take for 3 weeks, followed by 1 week without pills.
   The 28-pill pack has 21 "active" (6 brown, 5 white and 10 light yellow) pills (with hormones) to take for 3 weeks, followed by 1 week of reminder (light-green) pills (without hormones).
3. ALSO FIND:
   1) where on the pack to start taking pills.
   2) in what order to take the pills (follow the arrows)

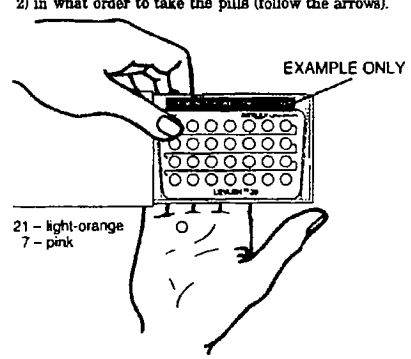
[See Figure at top of next column.]



4. BE SURE YOU HAVE READY AT ALL TIMES:
   ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam or sponge) to use as a back-up in case you miss pills.
   AN EXTRA, FULL PILL PACK.

LEVLEN® Tablets

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
   It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 21 OR 28 PILLS:
   The 21-pill pack has 21 "active" (light-orange) pills (with hormones) to take for 3 weeks, followed by 1 week without pills.
   The 28-pill pack has 21 "active" (light-orange) pills (with hormones) to take for 3 weeks, followed by 1 week of reminder (pink) pills (without hormones).
3. ALSO FIND:
   1) where on the pack to start taking pills.
   2) in what order to take the pills (follow the arrows).



4. BE SURE YOU HAVE READY AT ALL TIMES:
   ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam or sponge) to use as a back-up in case you miss pills.
   AN EXTRA, FULL PILL PACK.

WHEN TO START THE FIRST PACK OF PILLS

TRI-LEVLEN® Tablets

You have a choice for which day to start taking your first pack of pills. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

DAY 1 START:

1. Take the first "active" (brown) pill of the first pack during the first 24 hours of your period.
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

SUNDAY START:

1. Take the first "active" (brown) pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. Use another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

LEVLEN® Tablets

You have a choice for which day to start taking your first pack of pills. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

DAY 1 START:

1. Take the first "active" (light-orange) pill of the first pack during the first 24 hours of your period.
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

SUNDAY START:

1. Take the first "active" (light-orange) pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. Use another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

WHAT TO DO DURING THE MONTH

TRI-LEVLEN® and LEVLEN® Tablets

1. **TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**
   Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
   Do not skip pills even if you do not have sex very often.
2. **WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:**
   21 pills: Wait 7 days to start the next pack. You will probably have your period during that week. Be sure that no more than 7 days pass between 21-day packs.
   28 pills: Start the next pack on the day after your last "remainder" pill.
   Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

TRI-LEVLEN® Tablets

If you **MISS 1** (brown, white or light-yellow) "active" pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** (brown or white) "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:

1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. YOU MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

If you **MISS 2** (light-yellow) "active" pills in a row in **THE 3rd WEEK:**

1. ***If you are a Day 1 Starter:***
   THROW OUT the rest of the pill pack and start a new pack that same day.
   If you are a Sunday Starter:
   Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

If you **MISS 3 OR MORE** (brown, white or light-yellow) "active" pills in a row (during the first 3 weeks).

1. ***If you are a Day 1 Starter:***
   THROW OUT the rest of the pill pack and start a new pack that same day
   If you are a Sunday Starter:
   Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.

Continued on next page

Information on the Berlex products appearing here is based on the most current information available at the time of publication closing. Further information for these and other products may be obtained from the Medical Affairs Department, Berlex Laboratories, 300 Fairfield Road, Wayne, New Jersey 07470, 1-800-888-2407. Information on Betaseron and Fludara may be obtained from Berlex Laboratories, 15049 San Pablo Avenue, Richmond, California 94804-0016, 1-800-888-4112.

Berlex Laboratories—Cont.

3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS:
If you forget any of the 7 (light-green) "reminder" pills in Week 4:
THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method if you start your next pack on time.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:
Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

LEVLEN® Tablets
If you **MISS 1** (light-orange) "active" pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** (light-orange) "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

If you **MISS 2** (light-orange) "active" pills in a row in **THE 3rd WEEK:**
1. ***If you are a Day 1 Starter:***
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

If you **MISS 3 OR MORE** (light-orange) "active" pills in a row (during the first 3 weeks).
1. ***If you are a Day 1 Starter:***
THROW OUT the rest of the pill pack and start a new pack that same day
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS:
If you forget any of the 7 (pink) "reminder" pills in Week 4:
THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method if you start your next pack on time.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:
Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

PREGNANCY DUE TO PILL FAILURE
The incidence of pill failure resulting in pregnancy is approximately less than 1.0% if taken every day as directed, but more typical failure rates are less than 3.0%. If failure does occur, the risk to the fetus is minimal.

RISKS TO THE FETUS
If you do become pregnant while using oral contraceptives, the risk to the fetus is small, on the order of no more than one per thousand. You should, however, discuss the risks to the developing child with your doctor.

PREGNANCY AFTER STOPPING THE PILL
There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.
There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

OVERDOSAGE
Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your health-care provider or pharmacist.

OTHER INFORMATION
Your health-care provider will take a medical and family history before prescribing oral contraceptives and will examine you. You should be reexamined at least once a year. Be sure to inform your health-care provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your health-care provider, because this is a time to determine if there are early signs of side effects of oral-contraceptive use.
Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth-control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES
In addition to preventing pregnancy, use of oral contraceptives may provide certain benefits. They are:
- Menstrual cycles may become more regular.
- Blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other symptoms during menstruation may be encountered less frequently.
- Ovarian cysts may occur less frequently.
- Ectopic (tubal) pregnancy may occur less frequently.
- Noncancerous cysts or lumps in the breast may occur less frequently.
- Acute pelvic inflammatory disease may occur less frequently.
- Oral-contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth-control pills, ask your doctor or pharmacist. They have a more technical leaflet called the "Professional Labeling", which you may wish to read.

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Manufactured for:
BERLEX Laboratories, Wayne, NJ 07470
Revised Jan., 1994 60700-0
Revised Apr., 1993 60658-1

Shown in Product Identification Guide, page 306

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(800) 888-4112
Fludara for Injection Only:
15049 San Pablo Avenue
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BETASERON®
(Interferon beta-1b) ℞

DESCRIPTION
Betaseron® (Interferon beta-1b) is a purified, sterile, lyophilized protein product produced by recombinant DNA techniques and formulated for use by injection. Interferon beta-1b is manufactured by bacterial fermentation of a strain of *Escherichia coli* that bears a genetically engineered plasmid containing the gene for human interferon $beta_{ser17}$. The native gene was obtained from human fibroblasts and altered in a way that substitutes serine for the cysteine residue found at position 17. Interferon beta-1b is a highly purified protein that has 165 amino acids and an approximate molecular weight of 18,500 daltons. It does not include the carbohydrate side chains found in the natural material.
The specific activity of Betaseron is approximately 32 million international units (IU)/mg Interferon beta-1b. Each vial contains 0.3 mg (9.6 million IU) of Interferon beta-1b. The unit measurement is derived by comparing the antiviral activity of the product to the World Health Organization (WHO) reference standard of recombinant human interferon beta. Dextrose and Albumin Human, USP (15 mg each/vial) are added as stabilisers. Prior to 1993, a different analytical standard was used to determine potency. It assigned 54 million IU to 0.3 mg Interferon beta-1b.
Lyophilized Betaseron is a sterile, white to off-white powder intended for subcutaneous injection after reconstitution with the diluent supplied (Sodium Chloride, 0.54% Solution).

CLINICAL PHARMACOLOGY
General: Interferons are a family of naturally occurring proteins, which have molecular weights ranging from 15,000 to 21,000 daltons. Three major classes of interferons have been identified: alfa, beta, and gamma. Interferon beta-1b, interferon alfa, and interferon gamma have overlapping yet distinct biologic activities.[1-5] The activities of Interferon beta-1b are species-restricted and, therefore, the most pertinent pharmacologic information on Betaseron is derived from studies of human cells in culture and in humans.
Biologic Activities: Interferon beta-1b has been shown to possess both antiviral and immunoregulatory activities. The mechanisms by which Betaseron® (Interferon beta-1b) exerts its actions in multiple sclerosis (MS) are not clearly understood. However, it is known that the biologic response-modifying properties of Interferon beta-1b are mediated through its interactions with specific cell receptors found on the surface of human cells. The binding of Interferon beta-1b to these receptors induces the expression of a number of interferon-induced gene products (e.g., 2',5'-oligoadenylate synthetase, protein kinase, and indoleamine 2,3-dioxygenase) that are believed to be the mediators of the biological actions of Interferon beta-1b.[1,3,6-10] A number of these interferon-induced products have been readily measured in the serum and cellular fractions of blood collected from patients treated with Interferon beta-1b.[11,12]
Pharmacokinetics: Because serum concentrations of Interferon beta-1b are low or not detectable following subcutaneous administration of 0.25 mg (8 million IU) or less of Betaseron, pharmacokinetic information in patients with MS receiving the recommended dose of Betaseron is not available. Following single and multiple daily subcutaneous administrations of 0.5 mg (16 million IU) Betaseron to healthy volunteers (N = 12), serum Interferon beta-1b concentrations were generally below 100 IU/mL. Peak serum Interferon beta-1b concentrations occurred between 1 to 8 hours, with a mean peak serum interferon concentration of 40 IU/mL. Bioavailability, based on a total dose of 0.5 mg (16 million IU) Betaseron given as two subcutaneous injections at different sites, was approximately 50%.
After intravenous administration of Betaseron (0.006 mg [0.2 million IU] to 2.0 mg [64 million IU]), similar pharmacokinetic profiles were obtained from healthy volunteers (N = 12) and from patients with diseases other than MS (N = 142). In patients receiving single intravenous doses up to 2.0 mg (64 million IU), increases in serum concentrations were dose proportional. Mean serum clearance values ranged from 9.4 $mL/min \cdot kg^{-1}$ to 28.9 $mL/min \cdot kg^{-1}$ and were independent of dose. Mean terminal elimination half-life values ranged from 8.0 minutes to 4.3 hours and mean steady-state volume of distribution values ranged from 0.25 L/kg to 2.88 L/kg. Three-times-a-week intravenous dosing for 2 weeks resulted in no accumulation of Interferon beta-1b in the serum of patients. Pharmacokinetic parameters after single and multiple intravenous doses of Betaseron® (Interferon beta-1b) were comparable.
Clinical Trials: The effectiveness of Betaseron in relapsing-remitting MS was evaluated in a double-blind, multiclinic (11 sites: 4 Canadian and 7 United States), randomized, parallel, placebo-controlled clinical investigation of 2 years duration. The study enrolled MS patients, aged 18 to 50, who were ambulatory (Kurtzke expanded disability status scale [EDSS] of ≤ 5.5), exhibited a relapsing-remitting clinical course, met Poser's criteria[13] for clinically definite and/or laboratory supported definite MS and had experienced at least two exacerbations over 2 years preceding the trial without exacerbation in the preceding month. Patients who had received prior immunosuppressant therapy were excluded.
An exacerbation was defined, per protocol, as the appearance of a new clinical sign/symptom or the clinical worsening of a previous sign/symptom (one that had been stable for at least 30 days) that persisted for a minimum of 24 hours.

Wyeth-Ayerst Laboratories—Cont.

Budd-Chiari syndrome.
Acne.
Changes in libido.
Colitis.
Sickle-cell disease.
Cerebral-vascular disease with mitral valve prolapse.
Lupus-like syndromes.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

NONCONTRACEPTIVE HEALTH BENEFITS

The following noncontraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral-contraceptive formulations containing doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol.

Effects on menses:
Increased menstrual cycle regularity
Decreased blood loss and decreased incidence of iron deficiency anemia
Decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation:
Decreased incidence of functional ovarian cysts
Decreased incidence of ectopic pregnancies

Effects from long-term use:
Decreased incidence of fibroadenomas and fibrocystic disease of the breast
Decreased incidence of acute pelvic inflammatory disease
Decreased incidence of endometrial cancer
Decreased incidence of ovarian cancer

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, Nordette-21 must be taken exactly as directed and at intervals not exceeding 24 hours.

The dosage of Nordette-21 is one tablet daily for 21 consecutive days per menstrual cycle according to prescribed schedule. Tablets are then discontinued for 7 days (three weeks on, one week off).

It is recommended that Nordette-21 tablets be taken at the same time each day, preferably after the evening meal or at bedtime.

During the first cycle of medication, the patient is instructed to take one Nordette-21 tablet daily for twenty-one consecutive days, beginning on the first day (Day 1 Start) of her menstrual cycle or on the Sunday after her period begins (Sunday Start). (The first day of menstruation is day one.) The tablets are then discontinued for one week (7 days). Withdrawal bleeding should usually occur within 3 days following discontinuation of Nordette-21. (For Day 1 Start: If Nordette-21 is first taken later than the first day of the first menstrual cycle of medication or postpartum, contraceptive reliance should not be placed on Nordette-21 until after the first seven consecutive days of administration. For Sunday Start: Contraceptive reliance should not be placed on Nordette-21 until after the first seven consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered.)

The patient begins her next and all subsequent 21-day courses of Nordette-21 tablets on the same day of the week that she began her first course, following the same schedule: 21 days on—7 days off. She begins taking her tablets on the 8th day after discontinuance regardless of whether or not a menstrual period has occurred or is still in progress. Any time a new cycle of Nordette-21 is started later than the 8th day, the patient should be protected by another means of contraception until she has taken a tablet daily for seven consecutive days.

If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged the patient is advised to consult her physician. Although the occurrence of pregnancy is highly unlikely if Nordette-21 is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed one or more tablets or started taking them on a day later than she should have) the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

For additional patient instructions regarding missed pills, see the "WHAT TO DO IF YOU MISS PILLS" section in the **DETAILED PATIENT LABELING** for LO/OVRAL.

Any time the patient misses one or two tablets she should also use another method of contraception until she has taken a tablet daily for seven consecutive days. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence. While there is little likelihood of ovulation occurring if only one or two tablets are missed, the possibility of ovulation increases with each successive day that scheduled tablets are missed.

In the nonlactating mother, Nordette-21 may be initiated postpartum, for contraception. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered (see "Contraindications," "Warnings," and "Precautions" concerning thromboembolic disease). It is to be noted that early resumption of ovulation may occur if Parlodel® (bromocriptine mesylate) has been used for the prevention of lactation.

HOW SUPPLIED

Nordette®-21 Tablets (0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol) are available in 6 PILPAK® dispensers of 21 tablets each as follows: NDC 0008-0075, light-orange, round tablet marked "WYETH" and "75".

References available upon request.

Brief Summary Patient Package Insert: See Lo/Ovral.
DETAILED PATIENT LABELING: See Lo/Ovral.

Shown in Product Identification Guide, page 340

NORDETTE®-28 ℞

[nor-det'-28]
TABLETS
(levonorgestrel and ethinyl estradiol tablets)

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

21 light-orange Nordette tablets, each containing 0.15 mg of levonorgestrel (*d* (-)-13 beta-ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one), a totally synthetic progestogen, and 0.03 mg of ethinyl estradiol (19-nor-17α-pregna-1,3,5 (10)-trien-20-yne-3,17-diol), and 7 pink inert tablets. The inactive ingredients present are cellulose, D&C Red 30, FD&C Yellow 6, lactose, magnesium stearate, and polacrilin potassium.

CLINICAL PHARMACOLOGY

See NORDETTE®-21

INDICATIONS AND USAGE

See NORDETTE-21

CONTRAINDICATIONS

See NORDETTE-21

WARNINGS

See NORDETTE-21

PRECAUTIONS

See NORDETTE-21
Drug Interactions: See NORDETTE-21
Carcinogenesis: See NORDETTE-21
Nursing Mothers: See NORDETTE-21
Information for the Patient: See LO/OVRAL.

ADVERSE REACTIONS

See NORDETTE-21

OVERDOSAGE

See NORDETTE-21

NONCONTRACEPTIVE HEALTH BENEFITS

See NORDETTE-21

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, Nordette-28 must be taken exactly as directed and at intervals not exceeding 24 hours.

The dosage of Nordette-28 is one light-orange tablet daily for 21 consecutive days, followed by one pink inert tablet daily for 7 consecutive days, according to prescribed schedule.

It is recommended that tablets be taken at the same time each day, preferably after the evening meal or at bedtime.

During the first cycle of medication, the patient is instructed to begin taking Nordette-28 on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first tablet (light-orange) is taken that day. One light-orange tablet should be taken daily for 21 consecutive days, followed by one pink inert tablet daily for 7 consecutive days. Withdrawal bleeding should usually occur within three days following discontinuation of light-orange tablets. During the first cycle, contraceptive reliance should not be placed on Nordette-28 until a light-orange tablet has been taken daily for 7 consecutive days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient begins her next and all subsequent 28-day courses of tablets on the same day of the week (Sunday) on which she began her first course, following the same schedule: 21 days on light-orange tablets—7 days on pink inert tablets. If in any cycle the patient starts tablets later than the proper day, she should protect herself by using another method of birth control until she has taken a light-orange tablet daily for 7 consecutive days.

If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician. Although the occurrence of pregnancy is highly unlikely if Nordette-28 is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed one or more tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

For additional patient instructions regarding missed pills, see the "WHAT TO DO IF YOU MISS PILLS" section in the **DETAILED PATIENT LABELING** for LO/OVRAL.

Any time the patient misses two or more light-orange tablets, she should also use another method of contraception until she has taken a light-orange tablet daily for seven consecutive days. If the patient misses one or more pink tablets, she is still protected against pregnancy **provided** she begins taking light-orange tablets again on the proper day.

If breakthrough bleeding occurs following missed light-orange tablets, it will usually be transient and of no consequence. While there is little likelihood of ovulation occurring if only one or two light-orange tablets are missed, the possibility of ovulation increases with each successive day that scheduled light-orange tablets are missed.

In the nonlactating mother, Nordette-28 may be initiated postpartum, for contraception. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered (see "Contraindications", "Warnings", and "Precautions" concerning thromboembolic disease). It is to be noted that early resumption of ovulation may occur if Parlodel® (bromocriptine mesylate) has been used for the prevention of lactation.

HOW SUPPLIED

Nordette®-28 Tablets (0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol) are available in 6 PILPAK® dispensers, each containing 28 tablets as follows:
21 active tablets, NDC 0008-2533, light-orange, round tablet marked "WYETH" and "75".
7 inert tablets, NDC 0008-0486, pink, round tablet marked "WYETH" and "486".

ALSO AVAILABLE:
Nordette®-28 Tablets (0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol) are available in packages of 12 PILPAK® dispensers for clinic use only, each containing 28 tablets as follows:
21 active tablets, NDC 0008-2533, light-orange, round tablet marked "WYETH" and "75".
7 inert tablets, NDC 0008-0486, pink, round tablet marked "WYETH" and "486".

References available upon request.

Brief Summary Patient Package Insert: See LO/OVRAL.
DETAILED PATIENT LABELING: See LO/OVRAL.

HOW TO TAKE THE PILL
For Nordette-28 PILPAK® Dispenser, See LO/OVRAL.
For Nordette-28 Clinic Pilpak®, See below.

HOW TO TAKE THE PILL

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

IMPORTANT POINTS TO REMEMBER

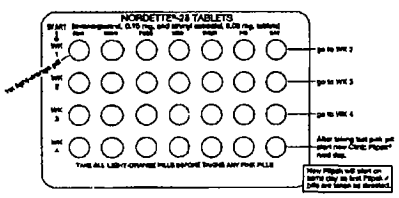
BEFORE YOU START TAKING YOUR PILLS:
1. BE SURE TO READ THESE DIRECTIONS:
Before you start taking your pills.
Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE EVERY DAY AT THE SAME TIME.
If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS.
If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these pills.
On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well. Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.

6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

NORDETTE®-21, OVRAL®, LO/OVRAL®, NORDETTE®-28, OVRAL®-28, AND LO/OVRAL®-28

BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 21 OR 28 PILLS:
The *21-pill pack* has 21 "active" white or light-orange pills (with hormones) to take for 3 weeks, followed by 1 week without pills.
The *28-pill pack* has 21 "active" white or light-orange pills (with hormones) to take for 3 weeks, followed by 1 week of reminder pink pills (without hormones).
3. ALSO FIND:
1) where on the pack to start taking the pills,
2) in what order to take the pills (follow the arrows), and
3) the week numbers as shown in the picture below.



4. BE SURE YOU HAVE READY AT ALL TIMES.
ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam or sponge) to use as a back-up in case you miss pills.
AND EXTRA, FULL PILL PACK

WHEN YOU START THE *FIRST* PACK OF PILLS:

For the 21-day pill pack you have two choices of which day to start taking your first pack of pills. (See **DAY 1 START** or **SUNDAY START** directions below.) Decide with your doctor or clinic which is the best day for you. The 28-day pill pack accommodates a **SUNDAY START** only. For either pill pack pick a time of day which will be easy to remember.
DAY 1 START:
These instructions are for the 21-day pill pack only. The 28-day pill pack does not accommodate a **DAY 1 START** dosage regimen.
1. Take the first "active" white or light-orange pill on the first pack during the *first 24 hours of your period.*
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.
SUNDAY START:
These instructions are for either the 21-day or the 28-day pill pack.
1. Take the first "active" white or light-orange pill of the first pack on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. *Use another method of birth control* as a back-up method if you have sex anytime from the Sunday you start you first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

WHAT TO DO DURING THE MONTH:

1. TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.
Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
Do not skip pills even if you do not have sex very often.
2. WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:
21 pills: Wait 7 days to start the next pack. You will probably have your period during that week. Be sure that no more than 7 days pass between 21-day packs.
28 pills: Start the next pack on the day after your last "reminder" pill.
Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** white or light-orange "active" pill:
1. Take it as soon as you remember. Take the pill at your regular time. This means you take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.
If you **MISS 2** white or light-orange "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the 7 *days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.
If you **MISS 2** white or light-orange "active" pills in a row in **THE 3rd WEEK:**
The ***Day 1 Starter*** instructions are for the 21-day pill pack only. The 28-day pill pack does not accommodate a **DAY 1 START** dosage regimen. The ***Sunday Starter*** instructions are for either the 21-day or 28-day pill pack.
1. ***If you are a Day 1 Starter:***
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday.
On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 *days* after you miss pills. You MUST use another method (such as condoms, foam, or sponge) as a back-up for those 7 days.
If you **MISS 3 OR MORE** white or light-orange "active" pills in a row (during the first 3 weeks):
The ***Day 1 Starter*** instructions are for the 21-day pill pack only. The 28-day pill pack does not accommodate a **DAY 1 START** dosage regimen. The ***Sunday Starter*** instructions are for either the 21-day or 28-day pill pack.
1. ***If you are a Day 1 Starter***
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter
Keep taking 1 pill every day until Sunday.
On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 *days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as back-up for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS:
If you forget any of the 7 pink "reminder" pills in Week 4:
THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method if you start your next pack on time.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:
Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE PILL EACH DAY until you can reach your doctor or clinic.

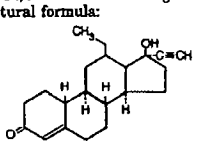
OVRETTE®
Ovrette is administered on a continuous daily dosage schedule, one tablet daily each day, every day of the year. Take the first tablet on the first day of your menstrual period. Tablets should be taken at the same time every day, without interruption, whether bleeding occurs or not. If bleeding is prolonged (more than 8 days) or unusually heavy, you should contact your doctor.
Forgotten pills
The risk of pregnancy increases with each tablet missed. Therefore, it is very important that you take one tablet daily as directed. If you miss one tablet, take it as soon as you remember and also take your next tablet at the regular time. If you miss two tablets, take one of the missed tablets as soon as you remember, as well as your regular tablet for that day at the proper time. Furthermore, you should use another method of birth control in addition to taking Ovrette until you have taken fourteen days (2 weeks) of medication.
If more than two tablets have been missed, Ovrette should be discontinued immediately and another method of birth control used until the start of your next menstrual period. Then you may resume taking Ovrette.

Pregnancy due to pill failure
The incidence of pill failure resulting in pregnancy is approximately less than 1.0% if taken every day as directed, but more typical failure rates are less than 3.0%. If failure does occur, the risk to the fetus is minimal.
RISKS TO THE FETUS
If you do become pregnant while using oral contraceptives, the risk to the fetus is small, on the order of no more than one per thousand. You should, however, discuss the risks to the developing child with your doctor.
Pregnancy after stopping the pill
There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.
There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.
Overdosage
Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your health-care provider or pharmacist.
Other information
Your health-care provider will take a medical and family history before prescibing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health-care provider believes that it is appropriate to postpone it. You should be reexamined at least once a year. Be sure to inform your health-care provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your health-care provider, because this is a time to determine if there are early signs of side effects of oral-contraceptive use.
Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth-control pills.
HEALTH BENEFITS FROM ORAL CONTRACEPTIVES:
See LO/OVRAL.
Shown in the Product Indentification Guide, page 340

NORPLANT® SYSTEM
(levonorgestrel implants)

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
Prescribing Information

DESCRIPTION
The NORPLANT SYSTEM kit contains levonorgestrel implants, a set of six flexible closed capsules made of silicone rubber tubing (Silastic®, dimethylsiloxane/methylvinylsiloxane copolymer), each containing 36 mg of the progestin levonorgestrel contained in an insertion kit to facilitate implantation. The capsules are sealed with Silastic (polydimethylsiloxane) adhesive and sterilized. Each capsule is 2.4 mm in diameter and 34 mm in length. The capsules are inserted in a superficial plane beneath the skin of the upper arm.
Information contained herewith regarding safety and efficacy was derived from studies which used two slightly different Silastic tubing formulations. The formulation being used in the NORPLANT SYSTEM has slightly higher release rates of levonorgestrel and at least comparable efficacy.
Evidence indicates that the dose of levonorgestrel provided by the NORPLANT SYSTEM is initially about 85 mcg/day followed by a decline to about 50 mcg/day by 9 months and to about 35 mcg/day by 18 months with a further decline thereafter to about 30 mcg/day. The NORPLANT SYSTEM is a progestin-only product and does not contain estrogen.
Levonorgestrel, (d(-)-13-beta-ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one), the active ingredient in the NORPLANT SYSTEM, has a molecular weight of 312.46 and the following structural formula:



Levonorgestrel

CLINICAL PHARMACOLOGY
Levonorgestrel is a totally synthetic and biologically active progestin which exhibits no significant estrogenic activity and is highly progestational. The absolute configuration conforms to that of D-natural steroids. Levonorgestrel is not subjected to a "first-pass" effect and is virtually 100% bioavailable. Plasma concentrations average approximately 0.30 ng/mL over 5 years but are highly variable as a function of individual metabolism and body weight.
Diffusion of levonorgestrel through the wall of each capsule provides a continuous low dose of the progestin. Resulting blood levels are substantially below those generally observed

Continued on next page

parent, or guardian. After the vaccine is prepared, the immunizing dose of 0.2–0.3 mL is dropped on the cleansed surface of the skin, and the vaccine is administered percutaneously utilizing a sterile multiple-puncture disc. The multiple-puncture disc is a thin wafer-like stainless steel plate $\frac{7}{8}'' \times 1\frac{1}{8}''$, from which 36 points protrude. The disc is held by a magnet type holder. In this method a drop of vaccine is placed on the arm and spread with the wide edge of disc. The disc is placed gently over the vaccine and the magnet is centered. The arm is grasped firmly from underneath, tensing the skin appreciably. Downward pressure is applied on the magnet so the points of the disc are well buried in skin. With pressure still exerted, the disc is rocked forward and backward and from side to side several times. Pressure underneath the arm is then released and the magnetic is slid off the disc. In a successful procedure, the points remain in the skin. If the points are on top of the skin, the procedure must be repeated. Remove the disc after successful puncture and spread vaccine evenly over the puncture area with the wide edge of the disc. Discs should only be used once and discarded after autoclaving. Between individual vaccinations the magnet should be sterilized (see instructions for use provided with the device). Discs may be purchased separately from Organon Teknika Corporation, telephone number (800) 662-6842. After vaccination the vaccine should flow into the wounds and dry. No dressing is required; however, it is recommended that the site be kept dry for 24 hours. The patient should be advised that the vaccine contains live organisms. Although the vaccine will not survive in a dry state, infection of others is possible.

Reconstituted vaccine should be kept refrigerated, protected from exposure to light, and used within 2 hours. Vaccination should be repeated for those who remain tuberculin negative to 5TU of tuberculin after 2–3 months.

Pediatric Dose: In infants less than 1 month old the dosage of vaccine should be reduced by one half, by using 2 mL of sterile water when reconstituting. If a vaccinated infant remains tuberculin negative to 5TU on skin testing, and if indications for vaccination persist, the infant should receive a full dose after 1 year of age.

HOW SUPPLIED

TICE BCG vaccine is supplied in a box of one 2 mL ampule of TICE BCG. Each ampule contains 1 to 8×10^8 CFU, which is equivalent to approximately 50 mg (wet weight), as lyophilized (freeze-dried) powder, NDC 0052-0601-01.

STORAGE

Storage of the intact ampules of TICE BCG should be at refrigerated temperatures of 2–8°C (36–46°F). This agent contains live bacteria and should be protected from light. The product should not be used after the expiration date printed on the label.

REFERENCES

1. Guerin C: The history of BCG. In: Rosenthal SR (ed): BCG Vaccine: Tuberculosis-Cancer. Littleton, MA, PSG Publishing Co., Inc. 1980, pp. 35–43.
2. Kelley DR, Haaff E, Becich M, et al.: Prognostic value of purified protein derivative skin test and granuloma formation in patients treated with intravesical bacillus Calmette-Guerin. J Urol 1986; 135:268–271.
3. Brosman SA: The use of bacillus Calmette-Guerin in the therapy of bladder carcinoma in situ. J Urol 1985; 134:36–39.
4. DeKernion JB, Huang M. Linder A, et al.: The management of superficial bladder tumors and carcinoma in situ with intravesical bacillus Calmette-Guerin. J Urol 1985; 133:598–601.
5. Guinan P, Batenhorst R: BCG in the treatment of superficial bladder cancer (Abstract). J Urol 1987; 137:180A.
6. Soloway M, Perry A: Bacillus Calmette-Guerin for treatment of superficial transitional cell carcinoma of the bladder in patients who have failed thiotepa and/or mitomycin C. J Urol 1987; 137:871–873.
7. Morales A: Long-term results and complications of intracavitary bacillus Calmette-Guerin therapy for bladder cancer. J Urol 1984; 132:457–459.
8. Haaff E, Dresner SM, Ratliff TL, Catalona WJ: Two courses of intravesical bacillus Calmette-Guerin for transitional cell carcinoma of the bladder. J Urol 1986; 136:820–824.
9. Herr HW, Pinsky CM, Whitmore WF, et al.: Effect of intravesical bacillus Calmette-Guerin (BCG) on carcinoma in situ. Cancer 1983; 51:1323–1326.
10. Kelley DR, Ratliff T, Catalona WJ, et al.: Intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. Effect of bacillus Calmette-Guerin viability on treatment results. J Urol 1985; 134:48–53.
11. Schellhammer PF, Ladaga LE, Fillion MB: Bacillus Calmette-Guerin for therapy of superficial transitional cell carcinoma of the bladder. J Urol 1986; 135:261–264.
12. Lamm DL: BCG immunotherapy in bladder cancer. In: Urology Annual 1987. Vol. 1, Appleton & Lange, Norwalk, CT, 1987; pp. 67–86.
13. Lamm DL, Sarosdy MS, DeHaven JI: Percutaneous, oral, or intravesical BCG administration: What is the optimal route? EORTC Genitourinary Group Monograph 6: BCG in Superficial Bladder Cancer. Alan R. Liss, Inc., New York, NY, 1989; pp. 301–310.
14. Utz DC, Hanash KA, Farrow GM: The plight of the patient with carcinoma in situ of the bladder. J Urol 1970; 103: 160–164.
15. Herr HW, Pinsky CM, Whitmore WF Jr., et al.: Long-term effect of intravesical bacillus Calmette-Guerin on flat carcinoma in situ of the bladder. J Urol 1986; 135:265–267.
16. Romanus V: Tuberculosis in bacillus Calmette-Guerin immunized and unimmunized children in Sweden: a ten-year evaluation following the cessation of general bacillus Calmette-Guerin immunization of the newborn in 1975. Pediatr Infect Dis 1987; 6:272–280.
17. Smith PG: Case-control studies of the efficacy of BCG against tuberculosis. In: International Union Against Tuberculosis, Proceedings of the XXXVIth IUAT World Conference on Tuberculosis and Respiratory Diseases, Singapore. Professional Postgraduate Services, International, Japan, 1987; 73–79.
18. Padungchan S, Konjanart S, Kasiratta S, et al.: The effectiveness of BCG vaccination of the newborn against childhood tuberculosis in Bangkok. Bull WHO 1986; 64:247–258.
19. Tidjani O, Amedone A, ten Dam HG: The protective effect of BCG vaccination of the newborn against childhood tuberculosis in an African community. Tubercle 1986; 67:269–281.
20. Young TK, Hershfield ES: A case-control study to evaluate the effectiveness of mass neonatal BCG vaccination among Canadian Indians. Am J Public Health 1986; 76:783–786.
21. Shapiro C, Cook N, Evans D, et al.: A case-control study of BCG and childhood tuberculosis in Cali, Columbia. Int H Epidemiol 1985; 14:441–446.
22. Morbidity and Mortality Weekly Report 37, No. 43 1988; pp. 663–675.
23. Rawls WH, Lamm DL, Eyolfson MF: Septic complications in the use of bacillus Calmette-Guerin (BCG) for noninvasive transitional cell carcinoma. Presented at: 1988 Annual Meeting, American Urological Association, Boston, MA.
24. Lorin MI, Hsu KHK, Jacob SC: Treatment of tuberculosis in children. In: Symposium on anti-infective therapy. Pediatric Clinics of North America, 1983; 30:333–348.
25. Report of the Committee on the Control of Infectious Diseases. American Academy of Pediatrics 1988; 21st Edition.
26. Data on file. Organon Teknika Corporation/Biotechnology Research Institute, Rockville, MD.
27. Lamm DL, Steg A, Boccon-Gibod L, et al.: Complications of bacillus Calmette-Guerin immunotherapy: Review of 2602 patients and comparison of chemotherapy complications. EORTC Genitourinary Group Monograph 6: BCG in Superficial Bladder Cancer. Alan R. Liss, Inc., New York, NY, 1989; pp. 335–355.
28. Standard Therapy for Tuberculosis, 1985. Presented at: National Consensus Conference on Tuberculosis. Chest, 1985; 87 (Suppl):117S–124S.
29. Oates R, Siroky M: Nephrogenic adenoma of urinary bladder due to intravesical BCG therapy. J Urol 1986; 135:186.
30. Mande R: BCG Vaccination. Dawsons, London, 1968.
31. Griffith AH: Ten cases of BCG overdose treated with isoniazid. Tubercle 1963; 44:247–250.
32. Watkins SM: Unusual complications of BCG vaccination. Brit Med J 1971; 1:442.

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RM 034.2 Issue Date: March, 1994

CALDEROL®

[kal-dah 'rol]

(calcifediol capsules, USP)

HOW SUPPLIED

20 µg (white, soft elastic capsules) bottle of 60
50 µg (orange, soft elastic capsules) bottle of 60
Shown in Product Identification Guide, page 325

CORTROSYN®

Cosyntropin is α 1–24 corticotropin, a synthetic subunit of ACTH.

HOW SUPPLIED

Box containing: 10 Vials of Cortrosyn® (cosyntropin) for injection 0.25 mg
10 ampuls of solvent (sodium chloride for injection, USP)

COTAZYM®

[kōt 'a zīm]

(pancrelipase capsules, USP)

DESCRIPTION

Cotazym® (pancrelipase capsules, USP) is a powder containing enzymes, principally lipase, with amylase and protease obtained from the pancreas of the hog. Each capsule contains not less than:
Lipase—8,000 USP Units
Protease—30,000 USP Units
Amylase—30,000 USP Units
Precipitated calcium carbonate 25 mg.
Each capsule also contains the inactive ingredients: cornstarch, gelatin, magnesium stearate, talc, FD&C green #3, FD&C yellow #10 as coloring and titanium dioxide.

INDICATIONS AND USAGE

It is indicated in conditions where pancreatic enzymes are either absent or deficient with resultant inadequate fat digestion. Such conditions include but are not limited to chronic pancreatitis, pancreatectomy, cystic fibrosis and steatorrhea of diverse etiologies.

CONTRAINDICATIONS

Known hypersensitivity to pork protein.

PRECAUTIONS

In the event that capsules are opened for any reason care should be taken so that powder is not inhaled or spilled on hands since it may prove irritating to the skin or mucous membranes.

ADVERSE REACTIONS

No adverse reactions have been reported. It should be noted, however, that extremely high doses of exogenous pancreatic enzymes have been associated with hyperuricosuria and hyperuricemia.

DOSAGE AND ADMINISTRATION

One to three capsules just prior to each meal or snack. Individual cases may require higher dosage and dietery adjustment.

STORAGE

Not to exceed 25°C (77°F). Store in dry place when opened.

DISPENSE

In tight container as defined in the USP.

SUPPLIED

Cotazym capsules (regular) bottles of 100 and 500.
NDC # 0052-0381-91, NDC # 0052-0381-95.
Shown in Product Identification Guide, page 325

COTAZYM®-S

[kōt 'a zīm-s]

(pancrelipase, USP)
Enteric coated spheres

Each capsule contains not less than:

5,000	USP Units of Lipase
20,000	USP Units of Protease
20,000	USP Units of Amylase

HOW SUPPLIED

Bottles of 100 capsules
Bottles of 500 capsules
Shown in Product Identification Guide, page 325

DESOGEN®

(desogestrel and ethinyl estradiol) Tablets

PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

Caution: Federal law prohibits dispensing without prescription.

DESCRIPTION

Desogen® 28 Tablets provide an oral contraceptive regimen of 21 white round tablets each containing 0.15 mg desogestrel (13-ethyl-11- methylene-18,19-dinor-17 alpha-pregn-4-en- 20-yn-17-ol) and 0.03 mg ethinyl estradiol (19-nor-17 alpha-pregna-1,3,5 (10)-trien-20-yne-3,17-diol). Inactive in-

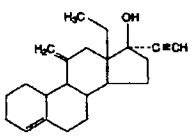
Continued on next page

Organon—Cont.

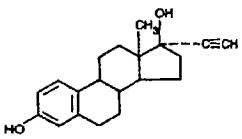
gredients include vitamin E, corn starch, povidone, stearic acid, colloidal silicon dioxide, lactose, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and talc. Desogen® 28 also contains 7 green round tablets containing the following inactive ingredients: lactose, corn starch, magnesium stearate, FD&C Blue No. 2 aluminum lake, ferric oxide, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and talc.

DESOGESTREL

DESOGESTREL



ETHINYL ESTRADIOL



CLINICAL PHARMACOLOGY

Pharmacodynamics

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus, which increase the difficulty of sperm entry into the uterus, and changes in the endometrium which reduce the likelihood of implantation.

Receptor binding studies, as well as studies in animals and humans, have shown that 3-keto-desogestrel, the biologically active metabolite of desogestrel, combines high progestational activity with minimal intrinsic androgenicity (91,92). Desogestrel, in combination with ethinyl estradiol, does not counteract the estrogen-induced increase in SHBG, resulting in lower serum levels of free testosterone (96–99).

Pharmacokinetics

Desogestrel is rapidly and almost completely absorbed and converted into 3-keto-desogestrel, its biologically active metabolite. Following oral administration, the relative bioavailability of desogestrel, as measured by serum levels of 3-keto-desogestrel, is approximately 84%.

In the third cycle of use after a single dose of Desogen®, maximum concentrations of 3-keto-desogestrel of 2,805±1,203 pg/mL (mean±SD) are reached at 1.4±0.8 hours. The area under the curve ($AUC_{0-\infty}$) is 33,858±11,043 pg/mL·hr after a single dose. At steady state, attained from at least day 19 onwards, maximum concentrations of 5,840±1,667 pg/mL are reached at 1.4±0.9 hours. The minimum plasma levels of 3-keto-desogestrel at steady state are 1,400±560 pg/mL. The AUC_{0-24} at steady state is 52,299±17,878 pg/mL·hr. The mean $AUC_{0-\infty}$ for 3-keto-desogestrel at single dose is significantly lower than the mean AUC_{0-24} at steady state. This indicates that the kinetics of 3-keto-desogestrel are non-linear due to an increase in binding of 3-keto-desogestrel to sex hormone-binding globulin in the cycle, attributed to increased sex hormone-binding globulin levels which are induced by the daily administration of ethinyl estradiol. Sex hormone-binding globulin levels increased significantly in the third treatment cycle from day 1 (150±64 nmol/L) to day 21 (230±59 nmol/L).

The elimination half-life for 3-keto-desogestrel is approximately 38±20 hours at steady state. In addition to 3-keto-desogestrel, other phase I metabolites are 3α-OH-desogestrel, 3β-OH-desogestrel, and 3α-OH-5α-H-desogestrel. These other metabolites are not known to have any pharmacologic effects, and are further converted in part by conjugation (phase II metabolism) into polar metabolites, mainly sulfates and glucuronides.

Ethinyl estradiol is rapidly and almost completely absorbed. In the third cycle of use after a single dose of Desogen®, the relative bioavailability is approximately 83%.

In the third cycle of use after a single dose of Desogen®, maximum concentrations of ethinyl estradiol of 95±34 pg/mL are reached at 1.5±0.8 hours. The $AUC_{0-\infty}$ is 1,471±268 pg/mL·hr after a single dose. At steady state, attained from at least day 19 onwards, maximum ethinyl estradiol concentrations of 141±48 pg/mL are reached at about 1.4±0.7 hours. The minimum serum levels of ethinyl estradiol at steady state are 24±8.3 pg/mL. The AUC_{0-24}, at steady state is 1,117±302 pg/mL·hr. The mean $AUC_{0-\infty}$ for ethinyl estradiol following a single dose during treatment cycle 3 does not significantly differ from the mean AUC_{0-24} at steady state. This finding indicates linear kinetics for ethinyl estradiol.

The elimination half-life is 26±6.8 hours at steady state. Ethinyl estradiol is subject to a significant degree of presystemic conjugation (phase II metabolism). Ethinyl estradiol escaping gut wall conjugation undergoes phase I metabolism and hepatic conjugation (phase II metabolism). Major phase I metabolites are 2-OH-ethinyl estradiol and 2-methoxy-ethinyl estradiol. Sulfate and glucuronide conjugates of both ethinyl estradiol and phase I metabolites, which are excreted in bile, can undergo enterohepatic circulation.

INDICATIONS AND USAGE

Desogen® Tablets are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Oral contraceptives are highly effective. Table I lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of these methods can result in lower failure rates.

TABLE I: LOWEST EXPECTED AND TYPICAL FAILURE RATES (%) DURING THE FIRST YEAR OF USE OF A CONTRACEPTIVE METHOD

Method	Lowest* Expected*	Typical**
Oral Contraceptives		
combined	0.1	3
progestin only	0.5	N/A
Diaphragm with spermicidal cream or jelly	6	18
Spermicides alone (foam, creams, jellies and vaginal suppositories)	3	21
Vaginal Sponge		
nulliparous	6	18
parous	9	28
IUD (medicated)	2	3
Implant		
capsules	0.04	0.04
rods	0.03	0.03
Condom without spermicide	2	12
Cervical Cap	6	18
Periodic abstinence (all methods)	1–9	20
Female sterilization	0.2	0.4
Male sterilization	0.1	0.15
No contraception (planned pregnancy)	85	85

Adapted from J. Trussell, et al. Table 1, ref. #1.

N/A—Data not available.

* The author's best estimate of the percentage of women expected to experience an accidental pregnancy among couples who initiate a method (not necessarily for the first time) and who use it consistently and correctly during the first year, if they do not stop for any other reason.

** This term represents "typical" couples who initiate use of a method (not necessarily for the first time), who experience an accidental pregnancy during the first year, if they do not stop use for any other reason.

In clinical trials with Desogen®, 2,004 subjects completed 19,181 cycles and a total of 12 pregnancies were reported. This represents an overall user-efficacy pregnancy rate of 0.81 woman-years. This rate includes patients who did not take the drug correctly.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who currently have the following conditions:

- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebral vascular or coronary artery disease
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Hepatic adenomas or carcinomas
- Known or suspected pregnancy

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with formulations of higher doses of estrogens and progestogens than those in common use today. The effect of long term use of the oral contraceptives with formulations of lower doses of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population (Adapted from refs. 2 and 3 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

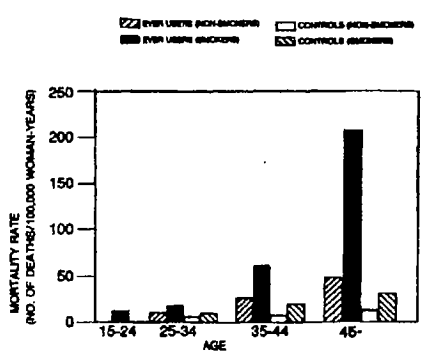
1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. Myocardial infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six (4-10). The risk is very low in women under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases (11). Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older among women who use oral contraceptives. (See Table II)

TABLE II: Circulatory disease mortality rates per 100,000 women-years by age, smoking status and oral contraceptive use



(Adapted from P.M. Layde and V. Beral, ref. #12.)

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity (13). In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism (14–18). Oral contraceptives have been shown to increase blood pressure among users (see section 9 in Warnings). Similar effects on risk factors have been associated

with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism
An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease (2,3,19–24). Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization (25). The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped (2).
A two to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives (9). The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions (26). If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four weeks after delivery in women who elect not to breast feed.

c. Cerebrovascular diseases
Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (> 35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, and smoking interacted to increase the risk of stroke (27–29).
In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension (30). The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension (30). The attributable risk is also greater in older women (3).

d. Dose-related risk of vascular disease from oral contraceptives
A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease (31–33). A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents (14–16). A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogens used in the contraceptives. The amount of both hormones should be considered in the choice of an oral contraceptive.
Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing 0.035 mg or less of estrogen.

e. Persistence of risk of vascular disease
There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years old who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups (8). In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small (34). However, both studies were performed with oral contraceptive formulations containing 0.050 mg or higher of estrogens.

TABLE III: ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE

Method of control and outcome	15–19	20–24	25–29	30–34	35–39	40–44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

*Deaths are birth related
**Deaths are method related

(Adapted from H.W. Ory, ref. #35.)

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE
One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table III). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth.
The observation of an increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's (35). Current clinical recommendation involves the use of lower estrogen dose formulations and a careful consideration of risk factors. In 1989, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of oral contraceptives in women 40 years of age and over. The committee concluded that although cardiovascular disease risk may be increased with oral contraceptive use after age 40 in healthy nonsmoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. The Committee recommended that the benefits of low-dose oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks.
Of course, older women, as all women who take oral contraceptives, should take an oral contraceptive which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and individual patient needs.
[See table above.]

3. CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS
Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. While there are conflicting reports most studies suggest that the use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk appears to be related to duration of use (36-43, 79-89).
Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women (45-48). However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

4. HEPATIC NEOPLASIA
Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use especially with oral contraceptives of higher dose (49). Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage (50,51).
Studies from Britain have shown an increased risk of developing hepatocellular carcinoma (52–54) in long-term (> 8 years) oral contraceptive users. However, these cancers are rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users

5. OCULAR LESIONS
There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY
Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy (56-57). The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned (55, 56, 58, 59), when oral contraceptives are taken inadvertently during early pregnancy.
The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.
It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out.

7. GALLBLADDER DISEASE
Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens (60,61). More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal (62-64). The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS
Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users (17). This effect has been shown to be directly related to estrogen dose (65). In general, progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents (17,66). In the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose (67). Because of these demonstrated effects, prediabetic and diabetic women should be carefully monitored while taking oral contraceptives.
A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS 1.a. and 1.d.), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

9. ELEVATED BLOOD PRESSURE
An increase in blood pressure has been reported in women taking oral contraceptives (68) and this increase is more likely in older oral contraceptive users (69) and with extended duration of use (61).
Data from the Royal College of General Practitioners (12) and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity.
Women with a history of hypertension or hypertension-related diseases, or renal disease (70) should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptive should be discontinued.
For most women, elevated blood pressure will return to normal after stopping oral contraceptives (69), and there is no difference in the occurrence of hypertension among former and never users (68,70,71).

10. HEADACHE
The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

Continued on next page

Parke-Davis—Cont.

MILONTIN® ℞
[mil"lŏn'tĭn]
(phensuximide)

DESCRIPTION
Milontin (phensuximide) is an anticonvulsant succinimide, chemically designated as N-methyl-2-phenylsuccinimide.
Each Milontin capsule contains 500 mg phensuximide. The capsule and band contain citric acid, USP; colloidal silicon dioxide, NF; D&C yellow No. 10, FD&C red No. 3, FD&C yellow No. 6, gelatin, NF; glyceryl monooleate, polyethylene glycol 200, sodium benzoate, NF; sodium lauryl sulfate, NF.

CLINICAL PHARMACOLOGY
Phensuximide suppresses the paroxysmal three-cycle-per-second spike and wave activity associated with lapses of consciousness which is common in absence (petit mal) seizures. The frequency of epileptiform attacks is reduced, apparently by depression of the motor cortex and elevation of the threshold of the central nervous system to convulsive stimuli.

INDICATIONS AND USAGE
Milontin is indicated for the control of absence (petit mal) seizures.

CONTRAINDICATION
Phensuximide should not be used in patients with a history of hypersensitivity to succinimides.

WARNINGS
Blood dyscrasias, including some with fatal outcome, have been reported to be associated with the use of succinimides; therefore, periodic blood counts should be performed. Should signs and/or symptoms of infection (eg sore throat, fever) develop, blood counts should be considered at that point.
It has been reported that succinimides have produced morphological and functional changes in animal liver. For this reason, phensuximide should be administered with extreme caution to patients with known liver or renal disease. Periodic urinalysis and liver function studies are advised for all patients receiving the drug.
Cases of systemic lupus erythematosus have been reported with the use of succinimides. The physician should be alert to this possibility.
Usage in pregnancy: Recent reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data is more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed anticonvulsants; less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs. The reports suggesting an elevated incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause-and-effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors, eg, genetic factors or the epileptic condition itself, may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.
The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

PRECAUTIONS
General:
Phensuximide, when used alone in mixed types of epilepsy, may increase the frequency of grand mal seizures in some patients.
As with other anticonvulsants, it is important to proceed slowly when increasing or decreasing dosage, as well as when adding or eliminating other medication. Abrupt withdrawal of anticonvulsant medication may precipitate absence (petit mal) status.
Information for Patients:
Phensuximide may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a motor vehicle or other such activity requiring alertness, therefore, the patient should be cautioned accordingly.
Patients taking phensuximide should be advised of the importance of adhering strictly to the prescribed regimen.
Patients should be instructed to promptly contact their physician if they develop signs and/or symptoms suggesting an infection (eg sore throat, fever).
Drug Interactions:
Since Milontin (phensuximide), as a member of the succinimide class, may interact with concurrently administered antiepileptic drugs, periodic serum level determinations of these drugs may be necessary.
Pregnancy:
See WARNINGS.

ADVERSE REACTIONS
Gastrointestinal System: Gastrointestinal symptoms, such as nausea, vomiting, and anorexia, occur frequently, but may be the result of overdosage.
Nervous System: Neurologic and sensory reactions reported during therapy with phensuximide have included drowsiness, dizziness, ataxia, headache, dreamlike state, and lethargy. Side effects, such as drowsiness and dizziness, may be relieved by a reduction in total dosage.
Integumentary System: Dermatologic manifestations reported to be associated with the administration of phensuximide have included pruritus, skin eruptions, erythema multiforme, Stevens-Johnson syndrome, erythematous rashes, and alopecia.
Genitourinary System: Genitourinary complications which have been reported include urinary frequency, renal damage, and hematuria.
Hemopoietic System: Hemopoietic complications associated with the administration of phensuximide include granulocytopenia, transient leukopenia, and pancytopenia with or without bone marrow suppression.
Musculoskeletal System: Muscular weakness.

OVERDOSAGE
Acute overdoses may produce nausea, vomiting, and CNS depression including coma with respiratory depression.
Treatment:
Treatment should include emesis (unless the patient is, or could rapidly become, obtunded, comatose, or convulsing) or gastric lavage, activated charcoal, cathartics and general supportive measures. Forced diuresis and exchange transfusions are ineffective.

DOSAGE AND ADMINISTRATION
Milontin is administered by the oral route in doses of 0.5 to 1 g two or three times daily. As with other anticonvulsant medication, the dosage should be adjusted to suit individual requirements. The total dosage, irrespective of age, may, therefore, vary between 1 and 3 g per day, the average being 1.5 g.
Milontin may be administered in combination with other anticonvulsants when other forms of epilepsy coexist with absence (petit mal).

HOW SUPPLIED
N 0071-0393-24 (Kapseal® 393)—Milontin capsules each containing 0.5 g phensuximide; bottles of 100.
© 1994, Warner-Lambert Co.
November 1994 0393G015
Shown in Product Identification Guide, page 327

NARDIL® ℞
(Phenelzine Sulfate Tablets, USP)

DESCRIPTION
Nardil® (phenelzine sulfate) belongs to the class of drugs known as monoamine oxidase (MAO) inhibitors. Chemically, it is phenethylhydrazine sulfate, a hydrazine derivative.
Each Nardil tablet for oral administration contains phenelzine sulfate equivalent to 15 mg of phenelzine base. Also contains: acacia, NF; calcium carbonate; carnauba wax, NF; corn-starch, NF; FD and C yellow No. 6; gelatin, NF; kaolin, USP; magnesium stearate, NF; mannitol, USP; pharmaceutical glaze, NF; povidone, USP; sucrose, NF; talc, USP; white wax, NF; white wheat flour.

CLINICAL PHARMACOLOGY
Monoamine oxidase is a complex enzyme system, widely distributed throughout the body. Drugs that inhibit monoamine oxidase in the laboratory are associated with a number of clinical effects. Thus, it is unknown whether MAO inhibition per se, other pharmacologic actions, or an interaction of both is responsible for the clinical effects observed. Therefore, the physician should become familiar with all the effects produced by drugs of this class.

INDICATIONS AND USAGE
Nardil has been found to be effective in depressed patients clinically characterized as "atypical," "nonendogenous," or "neurotic." These patients often have mixed anxiety and depression and phobic or hypochondriacal features. There is less conclusive evidence of its usefulness with severely depressed patients with endogenous features.
Nardil should rarely be the first antidepressant drug used. Rather, it is more suitable for use with patients who have failed to respond to the drugs more commonly used for these conditions.

CONTRAINDICATIONS
Nardil is contraindicated in patients with known sensitivity to the drug, pheochromocytoma, congestive heart failure, a history of liver disease, or abnormal liver function tests.
The potentiation of sympathomimetic substances and related compounds by MAO inhibitors may result in hypertensive crises (see WARNINGS). Therefore, patients being treated with Nardil should not take sympathomimetic drugs (including amphetamines, cocaine, methylphenidate, dopamine, epinephrine and norepinephrine) or related compounds (including methyldopa, L-dopa, L-tryptophan, L-tyrosine, and phenylalanine). Hypertensive crises during Nardil therapy may also be caused by the ingestion of foods with a high concentration of tyramine or dopamine. Therefore, patients being treated with Nardil should avoid high protein food that has undergone protein breakdown by aging, fermentation, pickling, smoking, or bacterial contamination; patients should also avoid cheeses (especially aged varieties), pickled herring, beer, wine, liver, yeast extract (including brewer's yeast in large quantities), dry sausage (including Genoa salami, hard salami, pepperoni, and Lebanon bologna), pods of broad beans (fava beans), and yogurt. Excessive amounts of caffeine and chocolate may also cause hypertensive reactions.
Nardil should not be used in combination with dextromethorphan or with CNS depressants such as alcohol and certain narcotics. Excitation, seizures, delirium, hyperpyrexia, circulatory collapse, coma, and death have been reported in patients receiving MAOI therapy who have been given a single dose of meperidine. Nardil should not be administered together with or in rapid succession to other MAO inhibitors because HYPERTENSIVE CRISES and convulsive seizures, fever, marked sweating, excitation, delirium, tremor, coma, and circulatory collapse may occur.
List of MAO Inhibitors

Generic Name	*Trademark*
pargyline hydrochloride	Eutonyl® (Abbot Laboratories)
pargyline hydrochloride and methylclothiazide	Eutron® (Abbot Laboratories)
furazolidone	Furoxone® (Roberts Pharmaceutical Corp)
isocarboxazid	Marplan® (Roche Laboratories)
procarbazine	Mutalane® (Roche Laboratories)
tranylcypromine	Parnate® (SmithKline Beecham Pharmaceuticals)

Nardil should also not be used in combination with buspirone HCl, since several cases of elevated blood pressure have been reported in patients taking MAO inhibitors who were then given buspirone HCl. At least 10 days should elapse between the discontinuation of Nardil and the institution of another antidepressant or buspirone HCl, or the discontinuation of another MAO inhibitor and the institution of Nardil.
There have been reports of serious reactions (including hyperthermia, rigidity, myoclonic movements and death) when fluoxetine has been combined with an MAO inhibitor. Therefore, Nardil should not be used in combination with fluoxetine. Allow at least five weeks between discontinuation of fluoxetine and initiation of Nardil and at least 10 days between discontinuation of Nardil and initiation of fluoxetine.
The combination of MAO inhibitors and tryptophan has been reported to cause behavioral and neurologic syndromes including disorientation, confusion, amnesia, delirium, agitation, hypomanic signs, ataxia, myoclonus, hyperreflexia, shivering, ocular oscillations, and Babinski signs.
The concurrent administration of an MAO inhibitor and bupropion hydrochloride (Wellbutrin®) is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion hydrochloride.
Patients taking Nardil should not undergo elective surgery requiring general anesthesia. Also, they should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors. The possible combined hypotensive effects of Nardil and spinal anesthesia should be kept in mind. Nardil should be discontinued at least 10 days prior to elective surgery.
MAO inhibitors, including Nardil, are contraindicated in patients receiving guanethidine.

WARNINGS
The most serious reactions to Nardil involve changes in blood pressure.
Hypertensive Crises: The most important reaction associated with Nardil administration is the occurrence of hypertensive crises, which have sometimes been fatal.
These crises are characterized by some or all of the following symptoms: occipital headache which may radiate frontally,

Organon—Cont.

DW, Stolley P, Warshauer ME, Shapiro S. Breast cancer before age 45 and oral contraceptive use: New Findings. Am. J. Epidemiol 1989; 129:269–280. 86. The UK National Case-Control Study Group, Oral contraceptive use and breast cancer risk in young women. Lancet 1989; 1:973–982. 87. Schlesselman JJ. Cancer of the breast and reproductive tract in relation to use of oral contraceptives. Contraception 1989; 40:1–38. 88. Vessey MP, McPherson K, Villard-Mackintosh L, Yeates D. Oral contraceptives and breast cancer: latest findings in a large cohort study. Br. J. Cancer 1989; 59:613–617. 89. Jick SS, Walker AM, Stergachis A, Jick H. Oral contraceptives and breast cancer. Br. J. Cancer 1989; 59:618–621. 90. Godsland, I et al. The effects of different formulations of oral contraceptive agents on lipid and carbohydrate metabolism. N Engl J Med 1990;323:1375–81. 91. Kloosterboer, HJ et al. Selectivity in progesterone and androgen receptor binding of progestogens used in oral contraception. Contraception, 1988;38:325–32. 92. Van der Vies, J and de Visser, J. Endocrinological studies with desogestrel. Arzneim. Forsch./Drug Res., 1983;33(I),2:231–6. 93. Data on file, Organon Inc.. 94. Fotherby, K. Oral contraceptives, lipids and cardiovascular diseases. Contraception, 1985; Vol. 31; 4:367–94. 95. Lawrence, DM et al. Reduced sex hormone binding globulin and derived free testosterone levels in women with severe acne. Clinical Endocrinology, 1981;15:87–91. 96. Cullberg, G et al. Effects of a low-dose desogestrel-ethinyl estradiol combination on hirsutism, androgens and sex hormone binding globulin in women with a polycystic ovary syndrome. Acta Obstet Gynecol Scand, 1985;64:195–202. 97. Jung-Hoffmann, C and Kuhl, H. Divergent effects of two low-dose oral contraceptives on sex hormone-binding globulin and free testosterone. AJOG, 1987;156:199–203. 98. Hammond, G et al. Serum steroid binding protein concentrations, distribution of progestogens, and bioavailability of testosterone during treatment with contraceptives containing desogestrel or levonorgestrel. Fertil. Steril., 1984;42:44–51. 99. Palatsi, R et al. Serum total and unbound testosterone and sex hormone binding globulin (SHBG) in female acne patients treated with two different oral contraceptives. Acta Derm Venereol, 1984; 64:517-23.

BRIEF SUMMARY
PATIENT PACKAGE INSERT
THIS PRODUCT (LIKE ALL ORAL CONTRACEPTIVES) IS INTENDED TO PREVENT PREGNANCY. IT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

Oral contraceptives, also known as "birth control pills" or "the pill", are taken to prevent pregnancy, and when taken correctly, have a failure rate of about 1% per year when used without missing any pills. The typical failure rate of large numbers of pill users is less than 3% per year when women who miss pills are included. For most women, oral contraceptives are also free of serious or unpleasant side effects. However, forgetting to take pills considerably increases the chances of pregnancy.

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be life-threatening or may cause temporary or permanent disability. The risks associated with taking oral contraceptives increase significantly if you:

- smoke
- have high blood pressure, diabetes, high cholesterol
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice or malignant or benign liver tumors

Although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy, non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, headache, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting, may subside within the first three months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and are young. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis) or lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack or angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes, and subsequent serious medical consequences.
2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the detailed patient labeling given to you with your supply of pills. Notify your doctor or clinic if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants and some antibiotics may decrease oral contraceptive effectiveness.

There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer. Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

Taking the combination pill provides some important non-contraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your doctor or clinic. Your doctor or clinic will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and your doctor or clinic believes that it is a good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient information labeling gives you further information which you should read and discuss with your doctor or clinic.

DETAILED PATIENT LABELING

THIS PRODUCT (LIKE ALL ORAL CONTRACEPTIVES) IS INTENDED TO PREVENT PREGNANCY. IT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

PLEASE NOTE: This labeling is revised from time to time as important new medical information becomes available. Therefore, please review this labeling carefully.

The following oral contraceptive product contains a combination of progestogen and estrogen, the two kinds of female hormones:

Desogen® 28 Day Regimen

Each white tablet contains 0.15 mg desogestrel and 0.030 mg ethinyl estradiol. Each green tablet contains inert ingredients.

INTRODUCTION

Any woman who considers using oral contraceptives (the birth control pill or the pill) should understand the benefits and risks of using this form of birth control. This patient labeling will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this labeling is not a replacement for a careful discussion between you and your doctor or clinic. You should discuss the information provided in this labeling with him or her, both when you first start taking the pill and during your revisits. You should also follow your doctor's or clinic's advice with regard to regular check-ups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives or "birth control pills" or "the pill" are used to prevent pregnancy and are more effective than other non-surgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% (1 pregnancy per 100 women per year of use) when used perfectly, without missing any pills. Typical failure rates are actually 3% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

In comparison, typical failure rates for other non-surgical methods of birth control during the first year of use are as follows:

IUD: 3%
Diaphragm with spermicides: 18%
Spermicides alone: 21%
Vaginal sponge: 18 to 28%
Implant: 0.03%
Condom alone: 12%
Periodic abstinence: 20%
No methods: 85%

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Some women should not use the pill. For example, you should not take the pill if you are pregnant or think you may be pregnant. You should also not use the pill if you have any of the following conditions:

- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes
- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor)
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy

Tell your doctor or clinic if you have ever had any of these conditions. Your doctor or clinic can recommend a safer method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your doctor or clinic if you have or have had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast x-ray or mammogram
- Diabetes
- Elevated cholesterol or triglycerides
- High blood pressure
- Migraine or other headaches or epilepsy
- Mental depression
- Gallbladder, heart or kidney disease
- History of scanty or irregular menstrual periods

Women with any of these conditions should be checked often by their doctor or clinic if they choose to use oral contraceptives.

Also, be sure to inform your doctor or clinic if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES

1. Risk of developing blood clots

Blood clots and blockage of blood vessels are one of the most serious side effects of taking oral contraceptives and can cause death or serious disability. In particular, a clot in one of the legs can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor or clinic about stopping oral contraceptives three to four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby. It is advisable to wait for at least four weeks after delivery if you are not breast feeding or four weeks after a second trimester abortion. If you are breast feeding, you should wait until you have weaned your child before using the pill. (See also the section on Breast Feeding in General Precautions.)

The risk of circulatory disease in oral contraceptive users may be higher in users of high dose pills and may be greater with longer duration of oral contraceptive use. In addition, some of these increased risks may continue for a number of years after stopping oral contraceptives. The risk of abnormal blood clotting increases with age in both users and non-users of oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages. For women aged 20 to 44 it is estimated that about 1 in 2,000 using oral contraceptives will be hospitalized each year because of abnormal clotting. Among nonusers in the same age group, about 1 in 20,000 would be hospitalized each year. For oral contraceptive users in general, it has been estimated that in women between the ages of 15 and 34 the risk of death due to a circulatory disorder is about 1 in 12,000 per year, whereas for nonusers the rate is about 1 in 50,000 per year. In the age group 35 to 44, the risk is estimated to be about 1 in 2,500 per year for oral contraceptive users and about 1 in 10,000 per year for nonusers.

2. Heart attacks and strokes

Oral contraceptives may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain) and

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